Supplemental Material 1: Study Protocol

Patient-Reported Barriers to Treatment of Wet Age Related Macular Degeneration a Qualitative Exploration

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Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness globally, and it is estimated that 6.4 million worldwide will be diagnosed with wet AMD in the year 2050 [1-3]. AMD is a chronic disease classified in two main types: dry and wet. Dry AMD caries in general a more favourable visual prognosis and counts for 80-85 % of all cases, whereas wet AMD, which progress from dry AMD, is a vision-threating disease and affects the remaining 15% to 20 % [2, 4]. AMD develops in the macula, the part of the eye that is especially important for seeing sharp images [5], and it causes central vision loss and makes objects appear blurry and distorted for the patients. As the name suggests, the disease is age-related, where the prevalence rise from 3.5% in those aged 55-59 years to 17.6 % in those aged above 85 years [6].

Every year, around 2300 patients are diagnosed with wet AMD in Denmark, and approximately 30,000 people live with the disease in Denmark today [7, 8], however it is expected that the number of patients will rise sharply as we get older and older [2, 9]. Fortunately, the introduction of intravitreal angiostatic therapy (anti-VEGF) about 17 years ago has revolutionized treatment options for wet AMD and halved the number of newly blind people over the age of 50 [7, 8, 10]. The treatment is often lifelong and require treatment at hospital with an injection into the affected eye every fourth to twelve week. Thus, the course of treatment can be debilitating and demanding especially among elderly and vulnerable patients. A Danish study found that up to 20% of patients opted out of treatment within the first two years for non-medical reasons [11]. These patients were above 90 years old and therefore, it is unknown how it is in younger patients, and it is unknown why the patients opted out of treatment. Varano et al. [12] found with a global survey that 84 % of patients treated with anti-VEGF were compliant with treatment; though, the reason for the remaining not compliant part was unclear.

Although we know that some patients do not adhere to the recommended treatment regime for wet AMD, it is poorly understood if they stop or omit treatment due to barriers like e.g. lack of knowledge of the disease, the treatment itself, distance from home to hospital or the commute to the many visits at the hospital etc. It is essential to understand the patient group and to fill this crucial gap of knowledge by exploring in depth which barriers they meet in the treatment course.

Aim

The aim of this non-interventional, explorative interview-based study was to explore patient-reported barriers of receiving recommended treatment for wet AMD in Denmark, and to examine if the barriers were modifiable, thus we can prevent patients with wet AMD from interrupting their treatment, and thereby, reduce the risk of vision loss in the future.

Rationale:

Although we know that some patients do not adhere to recommended treatment regime for nAMD, it is undefined if

they stop or omit the treatment for a longer period due to barriers like lack of knowledge ofthe disease, delayed diagnosis, the treatment itself, distance from home to hospital or the commute to the many visits at the hospital.

Thus, it is essential to examine the barriers and if they are modifiable and whether individual treatmentcourses can be developed to prevent patients from interrupting their recommended treatment and, thereby, prevent a negatively affected long-term outcome in nAMD patients.

Methods:

We plan to conduct a qualitative study using semi-structured interviews, where the interview guide will be developed in collaboration with the PPI. The intention is to involve 20 patients with nAMD in an open- ended interview to report their experiences and barriers to be diagnosed and receive treatment (recruitment is described in Setting). The interviews will be used to develop WP1-B, as the patient-reportedbarriers identified in interviews will be used to build and refine the questionnaire.

Analyses:

The interview will be held as physical meetings or telephone interview that will be audio-recorded, transcribed and analysed using Framework analysis, where we will divide the patient's experiences and barriers into categories and themes. The analyses will be organized using the software system NVivo. Thefindings from the interviews will be discussed and interpreted with our PPI before the questionnaire in WP1-B will be developed and before publishing our findings.

Recruitment:

Patients from Departments of Ophthalmology at Odense University Hospital and Zealand University Hospital in Roskilde will be invited to participate in an interview (n=20) when they visit one of the two departments for scheduled eye examinations or intravitreal treatment for nAMD.

Expected journal publications:

We expect to achieve important findings of patients' barriers they experience related to the treatment ofnAMD and that our findings will result in a peer-reviewed publication aimed at high-class international journals

Limitations

Limitations are important to acknowledge. Patients are only recruited for the interview when they visit the hospital for treatment, and therefore we are limited by the fact that the patients who opt out of the recommended treatment regime do not participate in this study and contribute with their experiences. Maybe these patients are those who experience the most barriers to treatment.

On the other hand, we hope to reach these patients through the questionnaire survey in the quantitative part, although this is also limited by the fact that the questionnaire is primary sent out via e-boks. This can be a major

problem in elderly patients many of whom probably are exempted from receiving public mail in e-boks because of impaired vision and problems with reading. Maybe we can reach out to some of these patients by given them e.g. an iPad in the waiting room at the hospital, who can read out loud the questionnaire.

Novelty

In this study, we have patient involvement in form of an advisory board. In addition, we want to conduct patient interviews and ask all patients with nAMD in Denmark via a questionnaire about their challenges with the course of treatment. This study is thus unique of its kind, as no one has previously illuminated this area of the eye profession in just that way.

Likewise, we have the opportunity to extract registry data from an entire national cohort including e.g. every single event of injection, and look at the side effects of a treatment that are injected into thousands of eyes every day around the world.

Clinical impact and feasibility

Patient organizations and healthcare professionals will be informed of our findings through peer-reviewed journals and national and international conferences. This might help health professionals adjust the communication regarding the disease and thereby establish individual courses of treatment with patient involvement and balanced considerations between patient's personal circumstances and risk of low visual acuity. E.g., a solution could be further education of eye nurses, so they can provide the majority of the information that patients lack in connection with the course of treatment.

Ethics:

The study will be performed according to the tenets of the Helsinki Declaration. We will ensure that all permissions are obtained and regulations and ethical guidelines are followed and obtained prior to the study. All patients will be asked to provide informed consent and informed that they at any time can withdrawals their consent. Patients unable to provide written or verbal consent prior to participation will be excluded.

We will apply for permission to contact and invite patients with nAMD to participate in a qualitative study WP1-A and a questionnaire (WP1-B). Further, data are stored in secure systems with strict access control. Data from interviews and survey are stored in the safe solution *OPEN Analyse* and data from national registers are stored centrally in Statistical bureaus. All data management and analyses will be performed on data without the personal identification numbers (these will be replaced by project- specific IDs), and only anonymous or aggregated results will be presented. It will not be possible to identify individuals in any results from this project.

Setting:

This study originates from Open Patient data Explorative Network (OPEN), Odense University Hospital, and

Department of Clinical Research, University of Southern Denmark, with Departments of Ophthalmology at Odense University Hospital and Zealand University Hospital in Roskilde of Zealand as our clinical partners. The study population will consist of patients from the catchment areas of these two departments, which receive approximately 40 new patients with presumed nAMD each week. The location of the two hospitalsgives patients in the two regions approximately equal travel distance to the departments in which all treatment is performed. Likewise, the study population is considered a heterogeneous[13], representative sample of patients with nAMD, thus making it realistic to implement individual courses of the treatment.

Patient and Public Involvement:

To ensure patient and public involvement, we plan to invite five patients treated for nAMD from Odense University Hospital or Zealand University Hospital, Roskilde, three nurses working with patient in treatment for nAMD at the hospital and three private consultant ophthalmologist to partake in a continuous advisory board throughout the study period (PPI). The recruitment into the board has already started, and the first introductory meeting has been held. The project idea has been presented,and comments from the participants are accounted for in the described study plan. We intend to invite more participants to the board when the project start.

We expect the PPI to offer the perspectives from primary care since they are the ophthalmologist that patients meet first after they experienced symptoms and from the patient's perspectives to ensure that thestudy is relevant and following the patient's experiences and expectations.

The PPI will be included in all phases of the research process, from defining the research questions and outcomes and defining the questions for the interview and questionnaire and interpreting the data. Since the target group for this study is patients who potentially can have a low visual acuity, it may be a problemto recruit patients through letter or mail. Therefore, it is important for us that the PPI is involved in the discussion on the recruitment of patients. We expect the PPI to evaluate whether it will work for the patients to be recruited to the study through an audio file or podcast.

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