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A Case of Age Related Macular Degeneration Responding to a Statin – Perspective for a New Treatment

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Authors' contributions

This work was carried out in collaboration between both authors. Author HG wrote the first draft of the manuscript. Authors HG and LLH managed the literature searches. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

The newly started use of atorvastatin eliminated the need for further intravitreal injections of ranibizumab for 37 months in a case of wet form of age related macular degeneration(AMD). Repeated optical coherence tomographic examinations documented the absence of intra- or subretinal fluid. The known effects of statins on endothelial function might also improve retinal capillary endothelial function and reduce or eliminate fluid leakage into the intra- or subretinal space. This would intervene earlier in one important disease mechanism of AMD than the injection of anti-VEGF therapies. A randomized study is necessary to prove this hypothesis.

Keywords: Age related macular degeneration (AMD); intravitreal injections; atorvastatin; ranibizumab; bevacizumab; subretinal fluid; vascular endothelial growth factor (VEGF).

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1. INTRODUCTION

Age-related macular degeneration (AMD) is considered the leading cause of severe and irreversible visual loss world-wide. Vascular endothelial growth factor (VEGF) has an important role in the pathophysiology of neovascular AMD and inhibition of VEGF by intraocular injection of a monoclonal antibody to VEGF has been shown to improve the natural course of the disease [1]. Intraocular injections however are complex, costly and not without risk. The major risk is endophthalmitis (1 in 1000-2000 Injections) which always requires a surgical intervention. Also rare but less serious are intraocular bleeding, retinal detachment and increased intraocular pressure as a possible consequence in prolonged anti-VEGF therapy [1]. A noninvasive treatment modality that could reduce the number of necessary injections would be desirable – both for the convenience of the patient and for the financial stability of the health care system in an aging society.

2. CASE REPORT

The 66 y/o cardiologist 175 cm, 74 kg, never smoker, was well until four and a half years ago (Dec 2007) when he noticed – while working with his computer – that horizontal lines in the left lower eye field were no longer straight or parallel but wavy- a case of metamorphopsia.

An ophthalmological examination revealed the early stage of age related macular degeneration (AMD) with drusen and slight hyperpigmentation on both eyes. The best corrected visual acuity (BCVA) of the left eye was still 20/20 to 20/25, with no signs of choroidal neovascularization in fluorescein angiography.

The vision of the left eye deteriorated subjectively during the next months, and at presentation seven months later BCVA had dropped to 20/32. A diagnosis of the wet form of AMD in the left eye was established by fluorescein angiography with fluid exudation and choroidal neovascularization. There was no fluid exudation in the right eye. A first series of three intravitreal injections of 0.5 mg Ranibizumab (Lucentis®) was started in August 2008. The injections were followed by temporary resolution of the fluid for 4-6 weeks but then reappearance of fluid lead to metamorphopsia and decrease of BCVA down to 20/50 at its lowest value. From January 2009 until June 2010 nine additional injections of ranibizumab depending on intra- or subretinal fluid detected by spectral domain optical coherence tomography (SDOCT, HRA Heidelberg Instruments) were necessary to improve and stabilize BCVA. BCVA of the left eye was 20/25 at the end of this treatment series.

Taking into account the mechanisms of disease in AMD [2,3] and the mechanism of action of atorvastatin which aside from lowering LDL-cholesterol also improves endothelial function by a direct so called pleiotropic effect of the drug [4] the patient began in June 2010 on his own initiative to take atorvastatin 40 mg per os every other day. The intention was to decrease fluid leakage into the retina by improving choroidal endothelial function. Atorvastatin was started after the last of a total of twelve injection of ranibizumab on June 26th 2010; the dosage was arbitrary but of proven efficacy with respect to LDL-cholesterol reduction; the drug lowered the LDL-cholesterol from 120 mg/dl to 62 mg/dl. Since that time significant intraretinal or subretinal fluid did not recur. This was confirmed in five consecutive SDOCT examinations two, four, ten, thirteen and again seventeen months after the last ranibizumab injection. A small scar, but no evidence of a new choroidal neovascularization and a stable BCVA with 20/32-20/25 showed the stability of the left eye for now more than 21 months. In addition the patient reported that the metamorphopsia increased, when the statin treatment was omitted for a day or longer which could be again corrected by strict medication compliance. The elimination half-life of the HMCG-CoA Reductase inhibitor atorvastatin and its active metabolites has been determined to be around 13.4 hrs [5] – which might explain this effect.

An additional examination was performed in a different university department in July 2013, thirty seven months after the last injection of ranibizumab confirming stability of the results.

3. DISCUSSION

The beneficial effects of intravitreal injection of inhibitors of the VEGF on AMD are undisputed[1]. The role of statins in the prevention of AMD or in limiting the progression of the disease has been investigated in several large observational studies with neutral results [6,7] but also possible beneficial [8,9] or detrimental [10] effects have been reported in (post hoc defined) subgroups. A single randomized study examining the effect of simvastatin on progression in intermediate AMD observed a statistically marginal beneficial

effect [11]. This study – however not this latest update of the study - was included in a recent update of the 2012 Cochrane Review which identified only two randomized studies investigating the effects of statins in AMD, and concluded that the evidence from the currently available trials is at present insufficient to attribute statins a role in preventing or delaying the onset or the progression of AMD [12].

This case report however is not suggesting a role of statins for prevention or delaying the onset of the disease but suggests a new indication for statins in the treatment during the early phase of the wet form of AMD, where it may decrease or prevent the exudation of fluid from the retinal capillaries - probably due to the so called pleiotropic effects of statins on improvement of endothelial function [4]. The amount of intraretinal or subretinal fluid is one important factor that determines the need for further intraocular injections of the chosen antibody to VEGF. The course of this case suggests that atorvastatin very likely was the cause for stopping further fluid exudate and the stabilization of choroidal neovascularization in this early stage of wet AMD. The possibility to stop intravitreal injections with ranibizumab is very uncommon unless a scarring with considerable drop of BCVA to 20/100 or less has occurred. Mechanisms of AMD [2] and a Medical Progress Report on AMD [3] show that capillary endothelial dysfunction, lipid deposition and inflammatory processes might play a role in the disease process. These mechanisms are all favorably influenced by statins in patients with coronary heart disease (CHD) although their influence on retinal capillary vessels or choroidal neovascularization due to AMD in men is still unknown. In a rat model however a similar effect of statins on decreasing endothelial leakage was observed [13].

AMD is now the most common cause of untreatable blindness in the Western world, with a prevalence of 0.05% before the age of 50 years, increasing to 11.8% after 80 years of age [14]. Unless effective methods of prevention and treatment are found, the prevalence of AMD is expected to double in the coming decades because of the projected increase in aging populations [2,3].

Anti-VEGF therapies are a milestone in the treatment of neovascular AMD, as they are the first form of treatment that offers a chance of improved visual acuity [1,15]. However initial studies have now revealed that anti-VEGF treatment for AMD also has its limitations, with some persons not responding to the therapy [14] and a not negligible risk of endophthalmitis [16,17] especially if one takes into account the unforeseeable numbers of intravitreal injections. Although ranibizumab is cost-effective, according to generally accepted criteria [15] a less expensive and non-invasive treatment would be highly desirable.

This case history leads to several hypotheses and questions:

- The treatment with a statin (here with atorvastatin) in the early course of the wet form of AMD has a beneficial effect on the disease course by reducing intra-or subretinal fluid leakage possibly by statin induced improved endothelial/capillary function of the choroidal vessels.
- The treatment with a statin allows to increase the intervals between necessary ranibizumab-injections or sometimes –like in this case report – may even obviate the need for ranibizumab-injections for more than three years.
- The prevention of fluid exudates intervenes earlier in one important disease mechanism of AMD than the injection of ranibizumab or other Anti-VEGF therapies like bevacizumab [17,18].

Observations from a single case do not allow a conclusion on causality. However the well-known effects of statins and the current knowledge of the AMD pathophysiology make it plausible, that a statin could play a beneficial role in the treatment of this disease. Beneficial pleiotropic effects on human arterial and venous endothelial function in larger vessels have recently been documented [4] and could possibly also play a role in the retinal vessels.

Randomized placebo controlled trials should be conducted to confirm or refute these hypotheses.

The chances for the successful performance of a randomized trial are excellent, the costs appear moderate. At present the use of statins has not been suggested [1,2,3,11,15,16] as a treatment option and expectations on the patients' or the referring ophthalmologists' sides are basically nonexistent. On the other hand the rather benign side effect profile of atorvastatin has been known for many years, where mild muscular complaints can occur in 10-15% of persons [17].

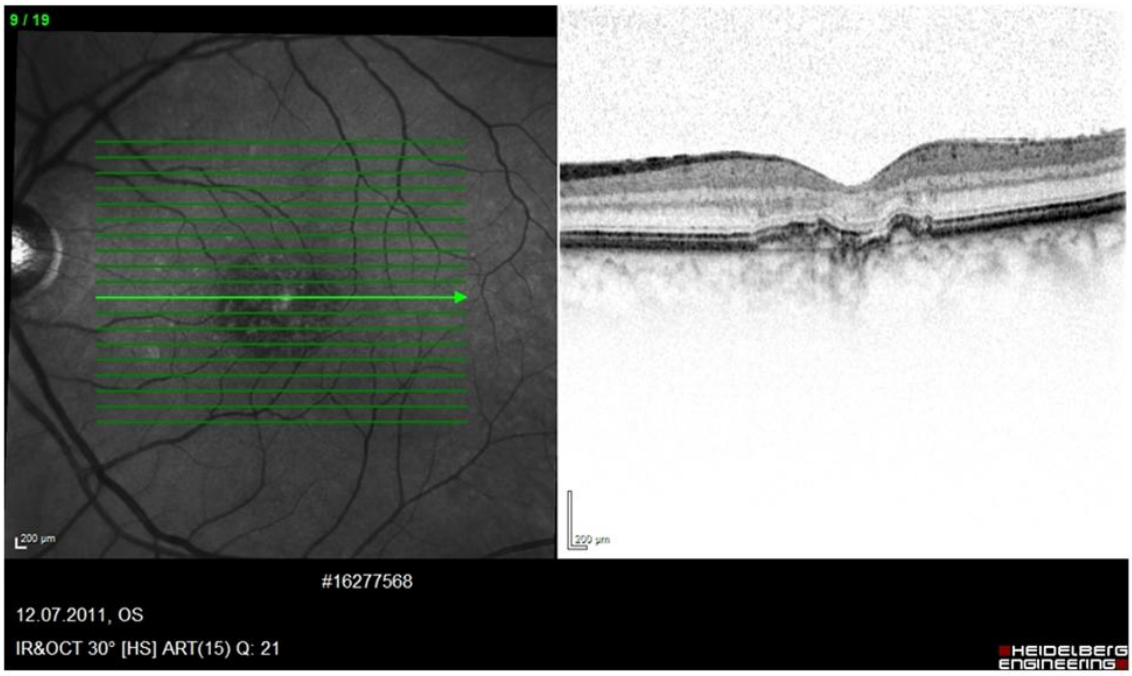

Fig. 1. After starting treatment with statins fluid did not relapse even after stopping ranibizumab. The SDOCT (Nov 22, 2011) demonstrates the stable scar without fluid after cessation of Ranibizumab for more than one year.

One additional benefit could be a statin induced decreased rate of cardiovascular events in patients undergoing treatment with Ranibizumab or Bevacizumab who possibly suffer from a mildly increased rate of such events [18,19,20]. There appears to be a correlation between the extent of coronary artery disease and the frequency of early age-related macular degeneration [21].

4. CONCLUSIONS

If a beneficial effect of atorvastatin on sub- or intraretinal fluid exudation in the wet form of AMD –as suggested from this case report - could be confirmed by a randomized study, this would be of great benefit for the patients and in addition this could lead to substantial savings for the health care system in many countries with long life expectancy of the population.

5. SUGGESTION FOR A RANDOMIZED CONTROLLED TRIAL

Statin naïve Patients with the wet form of AMD who are scheduled for intravitreal injections of ranibizumab or bevacizumab could be randomized to receive 40 mg of atorvastatin/day or placebo for 12 months in addition to the scheduled intravitreal injection.

The protocol and the primary endpoints could be similar as in the CATT research group study [22]:

- The amount of intra-or subretinal fluid (as measured by SDOCT) accumulated at four and eight weeks after the last intravitreal Anti-VEGF treatment (ranibizumab or bevacizumab).
- The number of re-injections of ranibizumab or bevacizumab appearing necessary by predetermined criteria in the atorvastatin vs. the placebo group over twelve months.
- The effect of Atorvastatin on BCVA assessed at baseline and after three, six, nine and twelve months.

CONSENT

Both authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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