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# Treatment of **choroidal neovascularization** in **wet AMD:** Comparative **experiences** and **new perspectives**

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— *Comparing our experiences with wet AMD management before and during the ongoing COVID-19 pandemic*

Intervention for neovascular, age-related macular degeneration (wet AMD) in the form of intravitreal injections of VEGF-inhibitors has dramatically improved visual outcomes for many with this common eye disease.<sup>1</sup> The burden of AMD care is considerable and constantly growing. Several preventive measures are available, including general advice to prolong our lives, such as avoiding tobacco, eating well, and exercising. More specific factors that may stop the progression from non-neovascular to neovascular AMD include eating green, leafy

vegetables and taking vitamin supplements.<sup>2</sup>

Favorable neovascular AMD outcomes require both prompt and repeated treatment as well as sustained care. This has been a challenge during the ongoing COVID-19 pandemic, but the lessons learned from the way this challenge has been met can help inform post-pandemic practice.

## Healthcare systems

In Denmark, the universal, tax-funded, public healthcare system is governed (and largely owned) by the state, which integrates the legislation,

oversight, insurance, and delivery of healthcare and social services. The role of private contractors in the Danish healthcare system is mainly within primary care. Long- and short-term contracts are made between the state and the private physicians, small group practices, or corporations within narrow fields. Emergency services, population-based responsibilities, and teaching obligations are restricted to government hospitals. In 2006, funding was granted for intravitreal, anti-VEGF therapy at a limited number of government hospitals as a pilot program. This

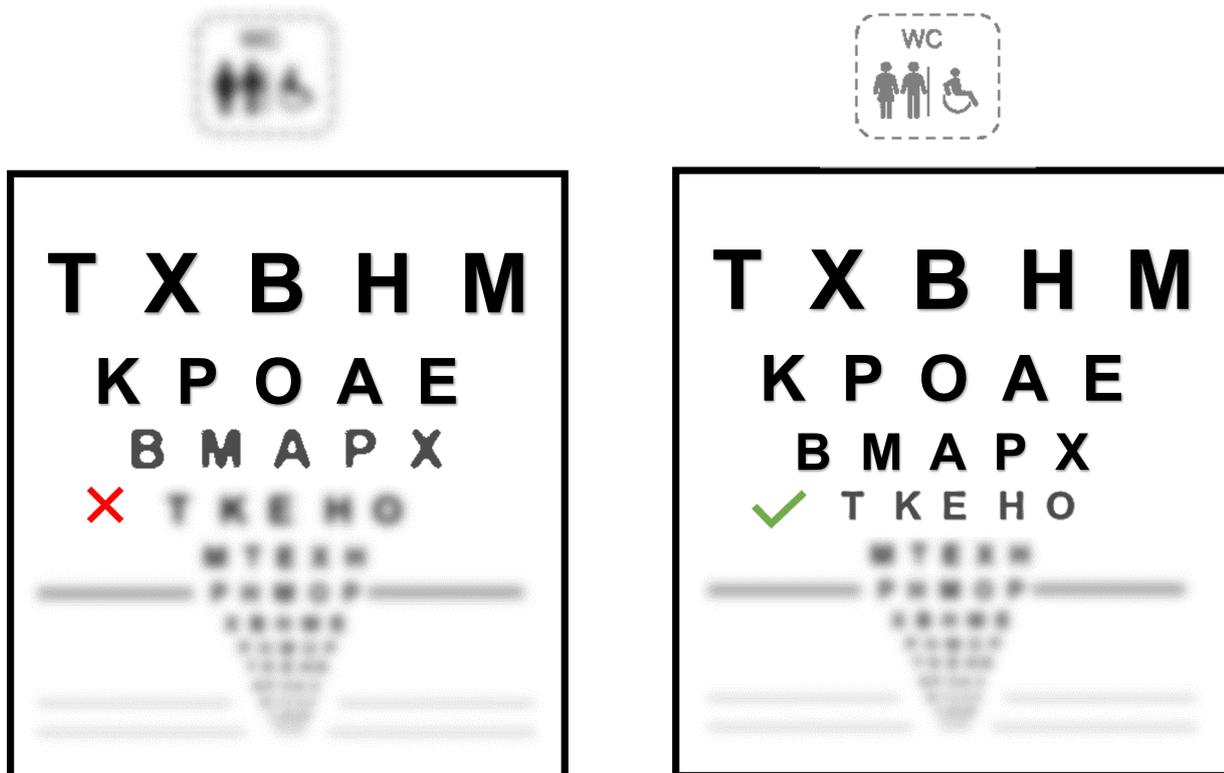
practice has not been changed. Patients with blurred vision and recent metamorphopsia are advised to consult a general ophthalmologist in a private practice or hospital emergency service. Both entities can refer patients suspected of having wet AMD to a hospital eye clinic, using either a 24-hour service or an elective, electronic referral procedure with optional image attachment. The latter is the recommended action.

Israel has a national healthcare system where all hospital services are financed by public funds and a nominal monthly membership fee.

Patients with acute eye problems can contact a local ophthalmologist, who will examine them within a few days and, if necessary, refer them to the emergency service of a hospital eye clinic. Alternatively, people can report to an emergency ward on their own, but there will be a charge if they do not bring a referral letter from their community physician. Once they have reached the hospital outpatient clinic, patients with active neovascular AMD can expect to receive a full work-up and treatment within one week and often within the first 24 hours.

**Is wet AMD an emergency?**

There is general agreement in industrialized countries that newly diagnosed neovascular AMD should be treated without undue delay to prevent further deterioration and recover as much vision as possible. However, practices differ in different healthcare systems, depending on the allocation of resources, insurance, logistics, and competition for patients. Intravitreal anti-VEGF injections are well tolerated, and millions of patients worldwide have received many injections without complications over the last 13 years. The rate of complications



**Figure 1. An illustration of a vision improvement by 5 ETDRS letters.** Figure 1A illustrates the vision of a hypothetical patient if treated day 1, when looking at ETDRS chart and a WC sign. Figure 1B illustrates the vision of the same patient, looking at the same objects, if treatment is delayed to day 16.

is on the order of 1 in 2,500-4,000 injections. Endophthalmitis is the most serious complication, but prompt professional management can preserve vision in many cases.

### Time to treatment matters

Age-related macular degeneration can quickly progress from a slumbering, asymptomatic condition to severe vision loss if the formation of new vessels under the retina suddenly rupture and bleed into the delicate neuronal tissue. There are other types of AMD with different forms of neovascularization, where the loss of vision is more insidious. Still, positive outcomes depend on a short time to treatment. The damage imparted by wet AMD can be fully developed within 14

days,<sup>3</sup> and the macula cannot repair itself, even if new vessel formation can be quenched. New pathological choroidal neovascularization penetrates both the retinal pigment epithelium and the retina itself, causing structural damage, as well as bleeding, exudation, and fibrosis. Together these outcomes require repeated follow-up and continued injections, which create a considerable burden for both the patient and physician.

There is ample evidence that early treatment of neovascular AMD can increase the chances of a favorable long-term outcome.<sup>4-7</sup> A study from Copenhagen found that reducing the delay to treatment from 16 to 1 day was associated with visual acuity that was 5 ETDRS letters better 3 months after the start of

treatment. This means that the very first injection for wet AMD is the most valuable injection, in terms of vision gained per injection.<sup>8</sup> Neovascular membranes in active growth increase in diameter by 10-18  $\mu\text{m}$  per day.<sup>9-10</sup> Thus, the younger and smaller the neovascularization, the better the visual outcome.<sup>11</sup> A study from Vienna found that a delay of 28 days from diagnosis to treatment was accompanied by loss of vision in 44% of patients.<sup>6</sup> In the UK, researchers found that regardless of baseline visual acuity, early treatment led to better visual outcomes.<sup>12</sup>

### Targeting new vessel activity

There is variation in the approach to neovascular AMD with very poor visual acuity at presentation. Poor visual acuity is commonly defined as best-corrected visual acuity worse than Snellen 0.1 or 0.05. Evidence to support the treatment of eyes with such poor visual acuity is relatively limited. However, data from randomized, controlled clinical trials has shown excellent vision gain across the range of baseline acuities, with no suggestion of a floor effect.<sup>15</sup> It must be emphasized, though, that the patients included in the pivotal trials had treatment-naïve, wet AMD with evidence of active vessel growth, leakage, and bleeding. Thus, active wet AMD with poor visual acuity



Figure 2. Several patients were injected at their home in Israel

at baseline merits treatment, especially if it affects the patient's better-seeing eye. Lesion activity, not visual acuity, is the primary indicator for treatment. Eye care professionals that know the impressive performance levels patients can achieve with 0.05 vision do not doubt that 0.05 it is worth fighting for. Fortunately, in both Israel and Denmark, patients with recent onset of the disease are entitled to free treatment, at the physician's discretion regardless of baseline visual acuity, without reimbursement issues.

### **What is the actual delay to treatment?**

Patients following a regular treatment regimen for wet AMD in one eye have good access to prompt treatment for wet AMD in their other eye, especially if both eyes are examined during their routine follow-ups. The people most at risk are those who do not know that they have wet AMD and misinterpret their symptoms. We commonly hear patient's saying: "It must be my glasses. I need to get some new ones." However, they may delay addressing this due to time or financial constraints. Unfortunately, people may already have irreversible vision loss in their first eye by the time they realize that something is wrong. And the list of potential delays does not stop there. It

should be noted that the term 'delay' is used here to denote latency, not to assign guilt, blame, or responsibility for factors that are outside the control of the patients or frontline healthcare workers. The delay to treatment can be categorized into five groups:

1. **Symptom delay:** The time from the onset of disease to realization that one may have a disease. Often caused by ones' tendency to assign functional limitations to external factors, such as insufficient lighting and too small print, or harmless conditions, such as age-related need for glasses. The category also includes the possibility that visual loss in one eye only is overlooked because the other eye is normal.
2. **Patient's delay from emergence of symptoms to action:** This includes the time it takes for the patient to get an appointment with a physician or other health care professional who can correctly evaluate the patient's problem.
3. **Physician's delay:** The gap in time from receiving the patient's request for an appointment until the diagnostic procedure has been completed and treatment offered.
4. **Referral delay:** The time it takes to get an appointment for treatment and perhaps additional work-up if it has to be administered at another clinic.
5. **Treatment delay:** The time from establishing the need to treat to the administration of treatment.

When the treatment for wet AMD was verteporfin-photodynamic therapy, the median delay from the patient first noticing blurred vision to contacting a general ophthalmologist was 45 days, according to a 2003 survey in the Greater Copenhagen Region (Haamann P, personal communication). In 2019, an informal survey of 48 patients presenting with wet AMD at the Department of Ophthalmology, Rigshospitalet found a median delay of 21 days from the first symptoms to the patient receiving intravitreal injections after being referred from a

general ophthalmologist. The reduction in patient delay has likely been driven by an increased awareness among both patients and professionals. In 2003, only 30% of adults in Western countries knew about AMD;<sup>13</sup> today, large hospitals now have thousands of AMD patients under continuous active care. The vast majority of incidents of AMD at Rigshospitalet receive their first injection on the same day, and most patients with bilateral disease are injected in both eyes on the same day. As there are no alternatives to repeated injections that are near marketing approval, the number

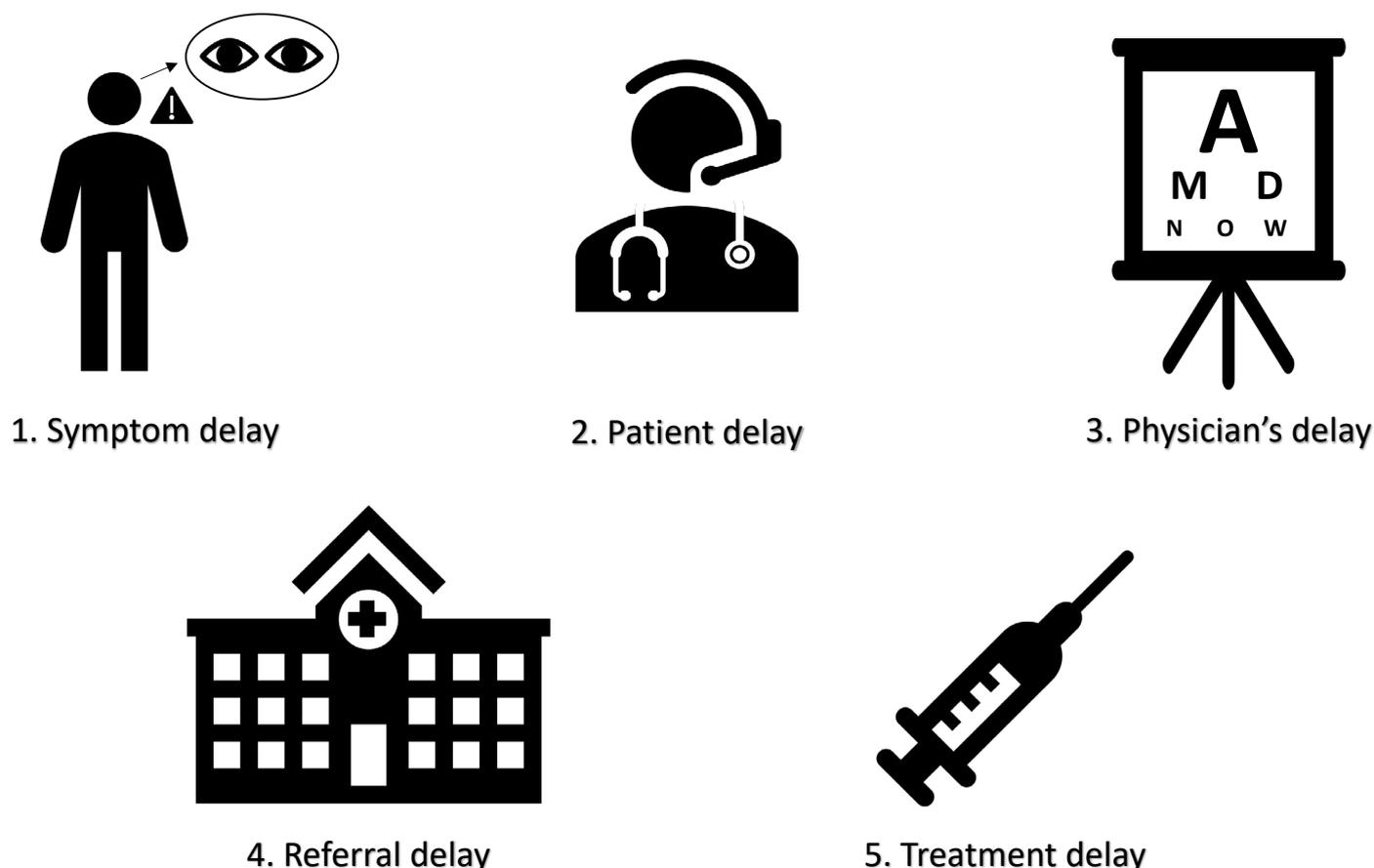


Figure 3. Types of latency or delay to treatment of wet AMD.

of injections is likely to increase over the next few years as the population ages.

### **Necessity is the mother of innovation**

During the COVID-19 pandemic, changes had to be made to the protocol. In Copenhagen, longer series of successive injections without intervening monitoring were prescribed to reduce the number of contacts and minimize the spread of the virus. This was merely an acceleration of changes to the protocol that were already underway in the eye

departments of Danish hospitals, the only places that can administer anti-VEGF injection therapy.

In Tel Aviv, a more innovative step has been taken to ensure that the most vulnerable of patients, could receive continued treatment. Elderly patients with underlying diseases were selected from hospital registries. A nurse and an ophthalmologist brought sterile kits and refrigerated injections to patients' homes and performed the procedure in an environment not unlike physicians' offices in many countries. Additionally,

office spaces outside the hospitals were quickly converted to temporary injection clinics. Patients were more willing to visit such places than hospitals, and compliance was high.

### **Is there room left to improve wet AMD management?**

We must strive for continual reduction in delays to treatment of wet AMD. Fundus photography and Optical Coherence Tomography (OCT) are becoming more broadly available as they can be performed in community-based clinics, general ophthalmologist offices, or by

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optometrists. This has expanded access to a qualified diagnosis. In the future, further flexibility can be gained by using external fundus imaging and remote evaluation by graders or artificial intelligence systems. The rapid exchange of electronic images and patient data is vastly under-explored. Both countries have recognized this issue and aim to address it with impending reforms.



**Figure 4. Representation of visual distortions experienced by those with newly diagnosed wet AMD.**

In conclusion, the differences between Israel and Denmark show that there is more than one way to deliver AMD care that effectively reduces the incidence of blindness.<sup>14</sup> Certain differences between the two countries can provide inspiration for how best practices can be combined. Policy accommodating technical innovations, promoting flexibility, and reducing cost could increase the efficacy of AMD treatment.



**Figure 5. Michaela and the technician outside a patient's home**

## REFERENCES

1. Philip J. Rosenfeld et al., Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 355:1419-31, 2006
2. Van Leeuwen, Redmer. Dietary Intake of Antioxidants and Risk of Age-Related Macular Degeneration. *JAMA: the journal of the American Medical Association*. 294.24 (2005): 3101-3107.
3. Adamis AP, Shima DT. The role of vascular endothelial growth factor in ocular health and disease. *Retina* 25:111-118, 2005.
4. Ying G et al. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. *Ophthalmology* 120:122-129, 2013.
5. Weber PA, Wiroszko BM, Xu X, Goss TF, and Zlateva G. Newly diagnosed exudative age-related macular degeneration treated with pegaptanib sodium monotherapy in US community-based practices: Medical chart review study. *BMC Ophthalmol* 10:0-9, 2010.
6. Rauch R, Weingessel B, MacA SM, Vecsei-Marlovits PV, Time to first treatment: The significance of early treatment of exudative age-related macular degeneration, *Retina*, 32:1260-1264, 2012.
7. Muether PS, Hermann MM, Koch K, and Fauser S. Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. *Graefes Arch Clin Exp Ophthalmol* 249:633-637, 2011.
8. Rasmussen A et al., Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. *Acta Ophthalmol* 93:616-620, 2015.
9. Vander JF, Morgan CM, Schatz H. Growth rate of subretinal neovascularization in age-related macular degeneration. *Ophthalmology* 96:1422-1429, 1989
10. Klein ML, Jorizzo PA, Watzke RC. Growth Features of Choroidal Neovascular Membranes in Age-related Macular Degeneration, *Ophthalmology*, 96:1416-1421, 1989.
11. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR. Subgroup Analysis of the MARINA Study of Ranibizumab in Neovascular Age-Related Macular Degeneration. *Ophthalmology* 114:246-252, 2007.
12. Lee AY et al., UK AMD EMR USERS GROUP REPORT V: Benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12, *Br J Ophthalmol*, 99:1045-1050, 2015.
13. Rosenthal B, Thompson B, Awareness of age-related macular degeneration in adults: the results of a large-scale international survey. *Optometry* 74:16-24, 2003.
14. Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010, *Am J Ophthalmol* 2012;153:209-213.
15. Tufail A, Margaron P, Guerin T, Larsen M. Visual benefit versus visual gain: what is the effect of baseline covariants in the treatment arm relative to the control arm? A pooled analysis of ANCHOR and MARINA. *Br J Ophthalmol* 104:672-677, 2020.