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# Efficacy and impact of antiangiogenic therapy for neovascular age-related macular degeneration

Information Monitoring Summary

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## Summary


Neovascular (wet) AMD is characterized by the abnormal formation of new blood vessels beneath the macula (neovascularization). These fragile vessels allow leakage of fluid or blood, leading to detached retina or hemorrhaging. The macula deteriorates and there may be rapid, severe loss of central vision.

Antiangiogenic drugs immediately reduce these fluids substantially. Eligible patients initially receive at least 3 consecutive monthly intravitreal injections. Therapy then continues on a monthly basis or as needed. Any improvement in visual acuity usually occurs during the first 3 months.

Two-year studies reveal spectacular results. With monthly injections, vision was stabilized or improved in 90% of cases, one-third of them showing significant improvement in visual acuity (VA). However, some 10% of patients continued to experience vision loss. On the other hand, very few people who remained untreated showed significant improvement in VA, and nearly half would deteriorate. After 2 years, treated patients had markedly better vision than untreated individuals.

Many people who are treated recover VA of at least 6/12. One study found that this proportion rose from 35% before therapy to 63% post therapy, while another study showed it increased from 15% to 42%. Moreover, the rate of severe visual impairment remained stable in treated individuals but increased in the untreated group.

Treatment efficacy appears to diminish somewhat over time. One research study covered a 4-year period. Compared to the results of 2-year studies, barely half as many subjects experienced visual gains (17%), while nearly twice as many experienced a loss in VA (23%). At the end of the 4$^{th}$ year, for various reasons, 45% of subjects were no longer being treated.

In patients with better baseline VA, treatment is more likely to be successful. However, many factors may render early treatment or continued therapy difficult (e.g. shortage of trained ophthalmologists; increasingly low ratio of ophthalmologists to population; long distance between patient's home and medical institution; poor health; the patient's or family's lack of knowledge about AMD and its consequences).

# Efficacy and impact of antiangiogenic therapy for neovascular age-related macular degeneration

Methods of treating neovascular (or “wet”) age-related macular degeneration (AMD) have greatly advanced in the last ten years. Antiangiogenic treatments, which substantially and immediately reduce fluids in or beneath the retina, are so far the most effective and promising therapy. Spectacular improvements have been achieved in a significant percentage of patients with wet AMD.

How can these results be interpreted in terms of vision rehabilitation? To answer this question, we first need to know how effective these treatments are. Do many people have improved vision following these treatments? Will they actually regain normal vision? What is the impact on the incidence and severity of visual impairment among people who are treated? And what do we know about the long-term effectiveness of these treatments and potential obstacles to their use? We turned to the literature to try to find the answers to these questions and give vision rehabilitation managers and clinicians a basis for assessing how these treatments can impact the services offered.

## 1. Age-related macular degeneration

Age-related macular degeneration is a chronic degenerative disease of the retina that begins after age 50. The World Health Organization describes it as the primary cause of blindness in industrialized countries, due to the population increase in the over-70 age group.

AMD causes deterioration of the macula, the area of the retina responsible for central vision and better visual acuity. It results in the gradual or sudden loss of central vision and affects a person’s capacity to perceive detail (e.g. facial features), read, and see from a distance [4].

There are two forms of AMD: dry and wet. The dry form, which is the more common and less serious, accounts for 85%-90% of cases diagnosed [18]. It is caused by the formation of drusen, tiny deposits that accumulate in one of the deep layers of the retina, Bruch’s membrane. According to Jager (2008), in the early stages of the disease, small drusen are observed as well as a few medium-sized ones. At the intermediate stage, at least one large druse and a number of medium-sized drusen are present. At the advanced stage, in addition to drusen, there is geographical atrophy extending towards the centre of the macula. This is actually damage to the layer of retinal pigment epithelium beneath the retina. The atrophy causes a lesion in the photoreceptors (image-receiving cells) in the central portion of the eye. Eventually these cells die, leaving “empty areas” or blind spots that damage central vision.

In the early stage of dry AMD, the person is usually asymptomatic; however, central vision loss gradually occurs during the advanced stage. The disease can evolve in a matter of months or may take as long as 10-20 years or even 30 [4; 18]; the individual may therefore gradually adapt to the resulting visual impairment [6]. Major vision loss is rare. However, the person may need a stronger reading light and find it more difficult to read, adjust to lighting variations, differentiate colors or perceive contrasts [4; 18]. There is no known treatment for dry AMD.

In certain cases, the dry form may develop into the wet form. Although only accounting for 10% to 15% of cases of AMD, wet form is the most severe. It is responsible for 80%-90% of the severe central vision loss associated with this disease [4; 18].

Wet AMD is characterized by the abnormal formation of new blood vessels under the macula. These new vessels are fragile and allow leaking of **1.** fluid under the macula, provoking detachment of the retina or **2.** blood, leading to hemorrhage [18]. All of this results in the degeneration and ultimately the destruction of photosensitive cells. The macula deteriorates rapidly, sometimes in just a few weeks or months [18]. Severe central vision loss can occur very fast, over a period ranging from a few weeks to two years [7; 18].

Prevalence of the disease increases with age. According to Jager et al. (2008), some 8% of people in the 43-54 age group have early stage AMD; this increases to 30% in people aged 75 and over [18]. According to various sources reported by Buhrmann et al. (2007), the prevalence of wet AMD is approximately 1.4% in the 65-74 age group, 7% in people aged 75 and over, 12% in people aged 80 and above, and 27% in individuals over 90 years old.

Buhrmann et al. (2007) estimated that in 2006, **1.** nearly 1 million Canadians had dry AMD, **2.** some 250 000 had advanced AMD, with geographical atrophy or neovascularization, and **3.** that these figures will have doubled by 2031 due to population aging [10]. Based on these authors' projections, the number of people with AMD-related vision loss will double between 2006 and 2031, going from 64 200 to 135 500. In 2007, based on estimations by Cruess et al. (2011), over 89 200 Canadians had vision loss caused by AMD [2].

In Canada, according to sources reported by Mandelcorn & Mandelcorn (2009), nearly 180 000 new cases of AMD without neovascularization and 17 000 new cases of AMD with neovascularization are recorded annually [22].

In the province of Quebec, according to 2004 estimates, slightly more than 37 000 people had AMD [20]. In 2007 and 2008, 8 076 severe new cases were detected [7].

## 2. Anti-angiogenic treatments for AMD: background

Arbour (2010) reports that the first treatment for wet AMD used the photocoagulation laser. However, the high failure rate and relapses in choroidal neovascularization (CNV) made researchers turn their attention to photodynamic therapy (PDT) with verteporfin (Visudyne). From 2000-2005, PDT was the standard treatment for predominant classic AMD with CNV (CNV complex located in the subretinal space). Subsequently, pegaptanib (Macugen) was approved in mid-2005. This was the first of the antiangiogenic drugs, which prevent formation of new blood vessels under the retina. Performing better than PDT, it could be used to treat all forms of CNV. Although these first two types of treatments proved effective in preventing severe vision loss, they only rarely (5% to 7%) achieved significant improvement in visual acuity [14; 16; 28; 29].

Not long after Macugen appeared on the pharmaceutical market, the preliminary results of studies on ranibizumab (Lucentis) were published. This drug proved superior to pegaptanib [9]. The results of small-scale clinical trials with bevacizumab (Avastin) were announced around the same time. Like pegaptanib, ranibizumab and bevacizumab are antiangiogenics. Vascular endothelial growth factor (VEGF) is a cytokine involved in the growth and permeability of neovessels. When the drug is repeatedly administered intravitreally, it inhibits this cytokine and its pathogenic effects, instantly and substantially reducing the fluids in or under the retina. This is currently the most promising and effective type of treatment for slowing the progression of wet AMD. In ophthalmology, antiangiogenic treatments are commonly referred to as anti-VEGFs, the term used here.

Ranibizumab (Lucentis) is the gold standard for treating wet AMD. It was approved in Canada in 2007. It is derived from the same parent molecule as bevacizumab (Avastin). Although the latter is also an anti-VEGF drug, it is intended for treating certain metastatic cancer. Avastin has not been approved as a treatment for wet AMD, but is widely used instead of Lucentis because it is much cheaper [22]. Many ophthalmologists use it for patients without insurance to cover the cost of Lucentis or living in a province that does not cover it [23]. The province of Quebec covers Lucentis [23].

## 3. Anti-VEGF treatments

For the Canadian expert consensus on optimal treatment of neovascular AMD, Cruess et al. (2012) reported six randomized, double-blind, multicentre studies that provide scientific evidence supporting the use of ranibizumab (Lucentis) [15]. The result was a consensus that treatment should be initiated with monthly intravitreal injections administered for 3 consecutive months. During this initial loading phase, there is rapid improvement.

The initial phase is followed by a further series of injections given monthly or as needed. In many scientific studies assessing treatment efficacy, injections were continued on a monthly basis. However, in actual clinical practice, this is not always possible. Patients

are generally monitored but treatment is only resumed if there is a sign of choroidal neovascularization (e.g. sub- or intra-retinal fluid, macular hemorrhage or intra-retinal macular edema, as observed or measured by optical coherence tomography; worsening of visual acuity) [8; 17; 19].

# 4. Efficacy of anti-VEGF treatments

## 4.1 Efficacy of monthly Lucentis therapy for 2 years

Many studies have evaluated the efficacy of Lucentis administered monthly for 2 years. They have been published by the following research groups: MARINA in 2006 [25], ANCHOR in 2009 [9] and CATT in 2012 [11]. Although these studies compare the efficacy of 0.3-mg and 0.5-mg doses, this article only deals with the results for 0.5 mg, which is the recommended dosage and the one that has proved most effective. To be admitted to one of the three studies, subjects had to have visual acuity of at least 6/95.

The efficacy of Lucentis was compared to that of a placebo (MARINA) or photodynamic treatment with verteporfin, referred to as PDT (ANCHOR).

Most changes occurred during the first 6 months [12; 17]; there were relatively few in the second year.

### 4.1.1 Global efficacy / impact on visual acuity

N.B. To make this article easier to read, where visual acuity is expressed as a number of letters (ETDRS scale), the number always refers to the mean and is rounded to the nearest unit. Standard deviations are not mentioned.

In the CATT study, the mean baseline visual acuity of subjects (pre-treatment) was 60 letters, which is approximately equivalent to 6/19 on the Snellen scale. In the ANCHOR study, it was 47 letters (6/38). After 2 years of treatment, a mean increase of 9 and 11 letters respectively was recorded. In comparison, individuals in the placebo and PDT groups lost approximately 10 letters. After 2 years of treatment, a difference of about 20 letters (4 lines on the Snellen chart) was therefore recorded between the visual acuity of treated subjects and those in the placebo or PDT groups.

In the PIER study, vision loss in the placebo group was even greater, with a mean reduction of 21 letters in 2 years [1].

Hence the treatments not only stabilize or improve vision but also prevent it from deteriorating. On average, individuals treated for 2 years have markedly better vision than those who are untreated.

### 4.1.2 Specific efficacy / stabilized, improved or deteriorated vision

Researchers define therapeutic success as a loss of fewer than 15 letters. In the ANCHOR, CATT and MARINA studies, after 2 years of treatment, 9 subjects out of 10

had lost fewer than 15 letters [9; 11; 25], which is well above the rate of 53% in the control group (MARINA) and the 66% in the PDT group (ANCHOR).

Among subjects who lost fewer than 15 letters, i.e. whose vision was at least stabilized, many gained at least 15 letters (visual acuity doubled or better). Thus, 30% to 41% of the subjects treated experienced a significant improvement in their vision [9; 11; 25]. Brown et al. (2009) even noted a gain of at least 30 letters (6 lines) in 14% of their subjects. By comparison, only 4% of subjects in the MARINA study placebo group showed significant improvement in their vision after 2 years.

In the MARINA study, significant deterioration in visual acuity (loss of at least 15 letters, i.e. reduction in visual acuity of at least half) was recorded for 9% to 10% of the subjects treated. Compared to this, 47% of subjects in the placebo group suffered a similar loss [25]. Moreover, after 2 years of treatment, only 3% of patients treated with Lucentis had severe vision loss (losing 30 letters or more since initiation of therapy) compared with 23% for the control group.

The treatment improved the vision of 3 to 4 persons out of 10 and stabilized vision in 5 to 6 subjects out of 10. On the other hand, vision continued to deteriorate in approximately 10% of subjects receiving treatment. By comparison, a very small number of untreated subjects had significant improvement in their vision while approximately half experienced a deterioration.

#### 4.1.3 Impact on proportion of individuals with vision ≥ 6/12

Baseline vision at the outset was equal to or better than 6/12 in 35% of subjects in the CATT group; this proportion rose to 63% at the end of the 2$^{nd}$ year of treatment. In the MARINA study, it went from 15% to 42% whereas it regressed from 15% to 6% in the control group. With the treatment, vision equal to or better than 6/12 was thus restored in a large percentage of patients; this was not the case in the untreated group.

#### 4.1.4 Impact on proportion of individuals with vision ≤ 6/60

At the outset, some 13% of subjects in the MARINA study had severe visual impairment (VA ≤ 6/60) as their baseline. At 24 months, this proportion remained stable in the treatment group (15%) but had considerably increased in the control group (48 %).

In the MARINA, ANCHOR and CATT studies, at the end of the 2$^{nd}$ year of monthly treatment, the percentage of subjects with severe visual impairment remained relatively stable compared to the baseline data [9; 11; 25]. The figure varied between 7% and 23%, depending on the study.

The treatment thus prevents an increase in the number of people with severe vision loss; this increase will occur when people are untreated.

## 4.2 Efficacy of treatments as needed

### 4.2.1 Efficacy of treatments as needed, tracked over 2 years

The CATT compared, for a 2-year period, the efficacy of Lucentis and Avastin therapies administered monthly or as needed, after the initial phase of 3 treatments in each case. The results showed that Avastin is not inferior to Lucentis. In addition, in both cases, subjects treated monthly had gained 2.4 letters more than those receiving treatments as needed [11].

The results of the PIER group showed that after the initial phase, a three-monthly treatment (i.e. at intervals of 3 months) is less effective than the continuous monthly dosage [24]. The gains achieved during the initial phase actually declined, going from +4.3 to -0.2 letters after 1 year.

Other studies reported by Cruess et al. (2012), such as those by the SAILOR, SUSTAIN and PrONTO groups, suggest that giving injections on an as-needed basis may reduce the initial visual gain; however, resuming monthly treatments could optimize the results.

The research by Hjelmqvist et al. (2011) in Sweden and Bandukwala et al. (2010) in Canada also examined the efficacy of Lucentis, but in a practical clinical context (injections as needed after the initial phase). These were prospective or retrospective, non-comparative, non-randomized and consecutive studies of patient records. Baseline VA was 58 letters (6/19) in the Hjelmqvist study and 52 letters (6/30) in the study by Bandukwala. After 1 year of treatment, 3 out of 4 subjects had stable visual acuity; slightly more than 1 in 10 had gained at least 15 letters (about 15% in Hjelmqvist and 11% in Bandukwala); a loss of at least 15 letters was recorded in the others (11% and 14%). The rate of subjects with a visual gain thus seems lower in these studies, in which injections were given as needed, than in those where they were given monthly.

Hjelmqvist et al. (2011) also evaluated the impact of treatment on patients' quality of life, using the NEI VFQ-25 questionnaire. Although at the 3$^{rd}$ month, a significant improvement was noted in certain spheres, at 12 months, the results had returned to baseline levels, with few exceptions (general vision, near vision activities).

### 4.2.2 Efficacy of treatments as needed, tracked for 3 years

In Sweden, Rung & Lovestam-Adrian (2013) evaluated prospectively, over a 3-year period, the results of treatments on an as-needed basis. Mean baseline visual acuity in the 51 subjects was around 53 letters (6/24). After the first 3 injections, a mean increase of 8 letters was recorded; this result is comparable to that in the other studies already mentioned. However, at the end of 3 years of as-needed treatments, a mean reduction of 9 letters (nearly 2 lines) was recorded, compared with baseline VA.

Specifically, 16 of the 51 subjects in this study (31%) had an improvement in their vision (57 letters before treatment vs. 69 letters at the end of the 3$^{rd}$ year, or 6/24 vs. 6/12). On

the other hand, 35 persons (61%) experienced a deterioration in VA, which diminished on average from 51 to 34 letters (6/30 to 6/60). Note that the criteria used by Rung & Lovestam-Adrian to gauge improvement or deterioration in vision were less stringent than those in the studies previously mentioned, so their results cannot be compared.

At the end of the 3rd year, the quality of life of patients as measured with NEI VFQ-25, had not improved. Certain spheres had even shown significant decrease (general health, ocular pain, distance activities, color vision, social functioning and role functioning [performance]) [26]. Moreover, in individuals whose vision had improved, only the "general vision" sphere had improved significantly; other spheres had remained stable.

Another Swedish study, this one by Frennesson & Nilsson (2012), evaluated retrospectively the impact of ranibizumab treatments administered as needed over a monitoring period of 3 years. The clinical cohort comprised 268 patients (312 eyes) with wet AMD; subjects had to have VA of at least 6/95 to be eligible for the treatments. Baseline visual acuity was 58 letters (6/19). Over the course of these 3 years, 65 patients were withdrawn from the study. Thirty (30) of these were removed for eye-health reasons (e.g. fibrosis), 8 for systemic reasons (e.g. stroke) and 1 due to moving out of the area. The remaining 26 died during the study.

A total of 79 individuals were followed-up for 36 months. At the end of the 3rd year, their mean VA was comparable to that measured prior to the treatments; VA in 77% of them had stabilized or significantly improved. However, 15 subjects were not included in this sub-sample because they had been withdrawn during the 3rd year for one of the above reasons. When their results were added to those for the 79 persons in the "3 years" group, the results were not so favourable; a mean loss of 4 letters was recorded.

### 4.2.3 Efficacy of as-needed treatments tracked over 4 years

In Denmark, Krüger Falk, Kemp & Sørensen (2013) conducted a 4-year retrospective study of patients with wet AMD treated with Lucentis (injections as needed after initial loading phase of 3 consecutive monthly injections). They had to have been followed for at least 15 months in order to be included in the study.

In average, baseline VA was around 6/24; at the last follow-up, it had diminished to 6/30 [19]. Specifically, 17% of subjects had gained at least 15 letters, 60% showed no significant change and 23% had lost at least 15 letters. In comparison to the 2-year studies by Bandukwala et al. (2010) and Hjelmqvist et al. (2011), around half as many subjects in this instance had a visual gain while nearly twice as many suffered a loss in acuity. Moreover, at the last examination, subjects with VA $\geq$ 6/12 were more numerous than at the outset (20% vs. 3%), as were those with VA < 6/120 (11% vs. 3%).

Note that 45% of patients were no longer being treated at the end of the 4th year. The reasons are discussed in section 5.

### 4.3 Efficacy of as-needed treatments in persons with severe visual impairment

People with better visual acuity at the outset, and whose lesion is therefore smaller and less detrimental to the fovea, have better chances of success with the treatment [4]. However, the vision of individuals with severe impairment may also improve.

In the study by Sørensen & Kemp (2011), 33 persons with wet AMD and visual acuity lower than 6/60 (median 6/120) were given Lucentis injections as needed. After an average treatment duration of 1 year, VA had improved in 76% of subjects, stabilized in 9% and deteriorated in 15% of cases. Median VA increased to 6/60 [27]. The improvement in certain subjects was spectacular, some of them having a post treatment VA of 6/12.

Bandukwala et al. (2010) also obtained good results in patients with severe visual impairment. After 1 year of treatment, nearly half of the 27 subjects with VA lower than 6/95 at the outset experienced an improvement of at least 15 letters.

However, the results obtained by Krüger Falk et al. (2013) suggest that excessively low vision at the start of therapy may render the prognosis less favourable. Their subjects who were deemed untreatable due to deterioration in their VA even after 3 to 6 injections, had lower baseline visual acuity than the others (6/38 vs. 6/24 for those undergoing active treatment). Moreover, certain authors have excluded subjects with VA lower than 6/95 from their studies [12; 24; 25].

## 5. Limitations of treatment and potential obstacles

In 2012, a consensus of experts for optimal treatment of neovascular AMD recommended among others that **1.** eligible persons treated with Lucentis should receive an initial treatment of at least 3 consecutive monthly injections; **2.** after this initial phase, monthly dosing should be given; if this is not possible, individualized regimen involving close monthly monitoring with optical coherence tomography is an alternative; **3.** treatment should be continued as long as the disease is active, unless the physician feels the structural damage is such that further treatment will not be beneficial [15].

Even though the scientific evidence shows that after the initial phase, injections should be continued monthly, in practice this is often not feasible. In the province of Quebec, as in many countries, the approach is therefore individualized. The patient is re-assessed regularly and intravitreal injections are administered as needed after the initial phase [3].

Many factors explain why wet AMD is not always treated according to the recommendations. The reasons involve ophthalmologists, patients and patients'

families. For example, access to initial diagnosis and treatment may be difficult because of **1.** a shortage of trained ophthalmologists and retina specialists; **2.** the diminishing ophthalmologist-to-population ratio; **3.** the general population lack of awareness about AMD and its consequences [15]. With the increase in the aging population, Cruess et al. (2012) speculate whether a sufficient number of trained ophthalmologists will be available to fulfill the demand. This concern also features in the report by Muzychka (2009), which predicts that the proportion of ophthalmologists in relation to the over-65 age group will have fallen by some 43% by 2024.

The more time that elapses between diagnosis and the start of treatment, the more the patient's vision deteriorates. In research by Arias et al. (2009), 27 out of 95 patients experienced visual loss during the average delay of 2.3 months (0.2 to 10.8 months in 95% of cases). Visual loss here means the patient went from one category of visual capacity to another, lower category, namely normal vision (VA > 6/12), mild visual impairment (6/12-6/24), moderate visual impairment (6/24-6/60), severe visual impairment (6/60-6/120) or almost total blindness (≤ 6/120). Specifically, at the 1$^{st}$ treatment, visual loss was recorded in 46% of subjects who, at time of diagnosis, had mild visual impairment. In addition, the number of persons who were almost totally blind nearly doubled, from 12 to 24. The longer the delay before treatment began, the more the vision deteriorated. A delay of over 3 months proved to be the threshold at which the correlation between treatment delay and visual loss was very high (0.6338) and significant (0.0001) [5]. This has a major impact, because the delay between the onset of symptoms and the start of treatment affects the efficacy of the therapy. This was demonstrated by Lim et al. (2012) in a study of 185 persons. Over a period of 6 months, subjects whose treatment was delayed 21 weeks or more were 2.6 times more likely to experience deterioration in their vision than those who waited 7 weeks or less. Although vision loss was slow for most individuals (about 1 line over a 110-day period), nearly 9% lost at least 1 line in 21 days. These authors recommend not delaying treatment for longer than 2 weeks in order to preserve as much of the patient's vision as possible [21]. This seems particularly true given that visual acuity is low to begin with (< 6/60); in these cases, the likelihood of improving VA was 80% when the wait was 7 weeks or less, compared to 25% when it exceeded 21 weeks.

Apart from the difficulty of accessing a trained ophthalmologist or retina specialist, a number of other factors can delay or interrupt treatment while the disease is still active [1; 8; 9; 12; 17; 19; 25]. These include the distance between the patient's home and the location where the physician practices (e.g. remote region, a move to another region; winter travel problems resulting in missed or postponed appointments; leaving temporarily to spend winter in a warmer climate); the patient's health (e.g. illness, insufficient energy for frequent treatments); a decision by the patient (e.g. perception that treatments are ineffective; not wanting any more injections); serious ocular and non-ocular side-effects associated with the treatment, though these are rare, etc.

The various studies listed reveal that treatment cessation rates are around 20%. For example, in the study by Hjelmqvist et al. (2011), an open, analytical and observational clinical trial, 21% of the 471 subjects stopped treatment during the first year. In one-third of these cases, the decision was made by the physician. Treatment of the remaining subjects was discontinued for a variety of reasons: too low visual acuity; lack of improvement; non-compliance with treatment; change in therapy; side effects; death; other reasons. In the 2-year studies by the PIER, MARINA and ANCHOR groups, treatment discontinuation rates varied between 14% and 20% [1; 9; 25]. In the 3-year study by Frennesson & Nilsson (2012), it was 24%. Depending on the study, deaths accounted for between 5% and 11% of discontinuations in treatment.

In the 4-year study by Krüger Falk, Kemp & Sørensen (2013), the rate of discontinuation of treatment at the end of the study was even higher, at around 47% of the 855 subjects. On average, these individuals had been followed-up for 16 months. Persons still being actively treated stood out from those whose treatment had been discontinued, for their higher mean baseline VA (6/24 vs. 6/30). The absence of active disease for 6 consecutive months justified the discontinuing of treatment in 45% of cases (mean VA 6/30 at baseline and last follow-up); 28% were deemed untreatable due to deterioration in their visual acuity despite the injections (6/38 baseline; 6/120 at last follow-up); 9% no longer wanted to be treated (6/30 baseline; 6/38 at last follow-up); other reasons were cited in 17% of cases.

## 6. Emerging treatments for neovascular AMD

At present, anti-VEGF treatments are the gold-standard therapy for neovascular AMD. Visual acuity in wet AMD patients can now be significantly improved or at least stabilized; however, to achieve and maintain these results, monthly injections appear to be required [22]. This is in itself a limitation. Treatment also has to be continued for long periods because anti-VEGF drugs only deactivate vascular endothelial growth factor in the subretinal tissue at time of treatment; they have no effect on the upstream events inducing its production.

Mandelcorn & Mandelcorn (2009) report that because choroidal neovascularization in AMD has a multifactored pathogenesis (inflammation, neo-angiogenesis, damage to extracellular matrix), many combinations of products with therapeutic properties combatting each of these mechanisms have been developed in the form of tritherapy. At present, these combination therapies benefit patients not so much by improving vision more than anti-VEGF therapy alone, but more by reducing the frequency with which treatments have to be resumed.

Meanwhile, as various authors report, different treatment approaches are being studied [13; 22]. These focus on the neuroprotection; the interference with the visual cycle by preventing, for example, the accumulation and absorption of retinol by the retinal

pigment epithelium; the action on stages in the development of choroidal neovascularization, in order to deliver longer-term benefit; the trap of anti-VEGF treatment, etc. Certain molecules are currently being investigated for possible clinical use with a view to developing treatments that are even more effective and durable.

## 7. Conclusion

Studies conducted over a 2-year period show spectacular results. In 9 cases out of 10, the treatments can stabilize or improve vision. On average, individuals treated for 2 years had markedly better vision than people who were not treated. However, approximately 10% of patients fail to respond to treatment and continue to get vision loss. Moreover, because the injections help above all to stabilize visual acuity, we are able to state with relative certainty that many people with a visual impairment at the outset will still have vision loss and require vision rehabilitation.

Only one study, which was conducted in a regular clinical setting, covered 4 years. The results are less positive than in the 2-year studies. What are the implications for people treated or monitored for 5-10 years? Further research is needed to answer this question.

Treatment does enable a significant percentage of patients to regain normal or quasi-normal visual acuity. However, initiating therapy as early as possible after the onset of the first symptoms of wet AMD seems to be key in optimizing efficacy. Many patients are likely to encounter delays, for various reasons; these include late diagnosis of the disease and difficulty accessing ophthalmology care and services promptly when symptoms first appear, due to the distances involved, the shortage of resources in some regions, health factors, and so on. Some patients only begin treatment or resume therapy when they already have incapacitating vision loss. The twofold challenge therefore remains of screening for wet AMD and offering treatment fast enough, despite the shortage of trained ophthalmologists and the falling ophthalmologist-to-population ratio.

Anti-VEGF treatments are probably already having, or soon will have, an impact on vision rehabilitation services for patients with neovascular AMD. However, as the studies show and regardless of the groundbreaking treatments now available, there will still be a number of individuals with functional incapacities for whom rehabilitation services are indicated. Meanwhile, extensive research is underway to develop even more effective treatments that may one day completely transform this disease and vision rehabilitation services for patients.

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