Belgian guidelines for the treatment of neovascular age-related macular degeneration

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Introduction

Age-related macular degeneration (AMD) is the most common cause of impaired vision in the developed countries. Of the total number of AMD patients, 10–20% have the neovascular form of the disease (nAMD). One third of patients with nAMD develop bilateral disease during 3–5 years.

Diagnosis

History taking & Clinical examination

Question your patients on risk factors such as a positive family history or smoking. A general history including current medications will identify systemic disease and possible contra-indications for anti-VEGF treatment.

Clinical examination upon diagnosis should always include bilateral testing of best-corrected visual acuity, slit-lamp examination, IOP measurement and fundoscopy. Patients should be instructed to self-monitor their vision and check the Amsler grid regularly between visits, also in the other eye. Advise about smoking cessation and healthy lifestyle should be given.

Diagnosis of nAMD should be based on multimodal imaging to choose the best therapeutic management.

Color Fundus photography

The fundus image gives an overview of the posterior pole and documents the neovascularization and other pathological correlates of nAMD such as drusen, pigment, atrophic changes, hemorrhage, tear of the RPE, … and is used for further follow-up.

Fluorescein angiography (FA)

FA was the main, and for many years, the only diagnostic and follow-up tool for AMD patients. Nowadays, many non-invasive techniques (such as OCT, OCTangiography, blue light auto-fluorescence imaging) can provide detailed anatomical information and precise functional data. In spite of this, FA continues to play a key role in the diagnostic process. The role of FA is to identify the presence, location and size of the neovascular complex as well as its dynamic features, such as perfusion and exudation.
When assessing a patient with clinical suspicion of nAMD, FA evaluation, if not contraindicated for systemic risks, is routinely performed upon diagnosis. It is an examination that can confirm the mere existence of a neovascularization and is also used to evaluate the location and extent. In addition, FA provides information about the dynamic exudative activity of the lesion. These features, particularly lesion size, have a well-recognized prognostic value and should be clarified in order to plan an appropriate treatment strategy.
An angiogram is also useful to detect specific forms of AMD that present a more aggressive natural history and requires modification of the therapeutic approach. Type 3 macular neovascularization (MNV) or retinal angiomatous proliferation (RAP) is characterized clinically by focal hemorrhage, edema and lipid exudates within retinal layers. In more advanced stages, a serous or vascularized pigment epithelial detachment (PED) is detectable.
During follow-up, FA may be repeated in the case of a sudden clinical worsening, inadequate therapeutic response, or in occurrence of hemorrhage or new PED but is not routinely indicated.

Optical coherence tomography (OCT)

OCT is a sensitive tool in the diagnosis of nAMD.
Advanced OCT permits high-speed retinal scanning that allows complete coverage of the macular area and is a major element in both initial diagnosis and management of patients with neovascular AMD.
OCT visualizes structural changes of the retina and RPE as a high-resolution optical 'histology', in a static mode, however, without identification of vascular features or any representation of dynamic processes such as perfusion or leakage.
OCT supports the diagnosis of neovascular AMD at initial presentation.
On top of that, OCT is currently the most frequently used tool in the long-term management of neovascular AMD. Comparisons of macular thickness and morphology over time allow a patient's response to treatment to be assessed.
Two types of assessment for neovascular activity can be distinguished: measurements (especially of central retinal thickness or CRT) and qualitative OCT observations. CRT has been the most common measurement used in clinical studies, however, treatment based on these measurements alone was invariably associated with reduced therapeutical benefit due to undertreatment. Currently, there is a large body of evidence that supports qualitative morphology-based OCT data as more sensitive than CRT measurements for detecting of activity of the neovascularization. Intraretinal cysts, subretinal fluid, subretinal "grey" zone (also called subretinal hyperreflective material SHRM) and RPE detachments are important signs of activity in the neovascular membrane, independent of CRT. All these qualitative features are usually considered as criteria for reinjection of anti-VEGF substances. Current SD-OCT or SS-OCT technologies which provide raster-scanning imaging, are very sensitive for detecting subtle morphological changes and, thus, permit early treatment of exudative recurrence. Newer AI algorithms for OCT analysis can quantify the amount of intraretinal fluid, subretinal fluid and sub RPE fluid and will provide very detailed information guiding treatment.
The concept of a 'zero tolerance' on OCT criteria is emerging, because of the rapid progression of exudative features and progressive loss of vision when initiation of treatment is delayed. However, persistent intraretinal cysts associated with atrophy should be considered signs of irreversible retinal

degeneration and should not trigger further retreatment. Although some authors suggest that a small amount of subretinal fluid can be accepted if a 4-week interval is maintained.
The common recommendation is, therefore, to monitor disease activity using OCT.
In summary, neovascular AMD is diagnosed based on leakage patterns found on FA. Optical coherence tomography, however, is more useful for following up patients after they have been diagnosed. Fluorescein angiography, if needed combined with ICG, is required to reassess the diagnosis in patients who do not respond to a given treatment. Optical coherence tomography provides quantitative evaluation of the disease and provides information about structural changes, particularly for outer retinal structures.

OCTangiography (OCT-A)
OCT-A can demonstrate the neovascularization and its localization in both retinal and choroidal layers in a non-invasive way. It can be useful upon diagnosis and during follow-up, and it may have an added value in cases where detection of active disease is not straightforward.

Indocyanine green angiography (ICG)
ICG may be necessary as an adjunctive study in the diagnosis and differential diagnosis of nAMD.
It is essential to detect specific forms of AMD that present a more aggressive natural history and requires modification of the therapeutic approach. Retinal angiomatous proliferation (RAP) is characterized clinically by focal hemorrhage, edema and lipid exudates within retinal layers. In more advanced stages, a serous or vascularized pigment epithelial detachment (PED) is detectable. ICG reveals the area of focal hypercyanescence arising from the deep capillary plexus forming the initial angiomatous lesion, which can break through the RPE and proliferate into the sub-RPE space. ICG is therefore vital to distinguish this lesion presentation and should be followed by OCT focused on the lesion site.
ICG can also more precisely delineate the boundaries of the neovascular type 1 and mixed neovascular membranes and thus give a better appreciation of their surface and location.
The other relevant example of a different subtype of exudative AMD is polypoidal choroidal vasculopathy (PCV). It is difficult to distinguish this entity clinically from type 1 MNV, even though, it presents more commonly with recurrent serous and hemorrhagic PED. FA shows an ill-defined type 1 leakage pattern, whereas ICG can delineate the polypoidal lesions in distinct detail and the branching vascular network.

Treatment

1. Intravitreal anti-VEGF

Anti-VEGF treatment should be initiated without delay after the onset of symptoms in order to promote prognosis. Initiating anti-VEGF treatment immediately or within a few days after the diagnosis versus after about 2-week delay may lead to better improvement of vision already detectable during the 3-month follow-up visit.
Treatment with intravitreal anti-VEGF injections should be considered for every eye with nAMD with BCVA ≧ 1/10.
Five different intravitreal anti-VEGF agents are currently available for treating nAMD.

Until now, no clinically significant differences in the efficacy and safety between the different anti-VEGF drugs have been shown in the treatment of nAMD during the first few years of follow-up (except for brolucizumab safety issues).
In case of recent cardiovascular or cerebrovascular event (within 3-6 months), anti-VEGF treatment can be considered after careful evaluation of the possible treatment related benefits and adverse effects.

1.1 Intravitreal Bevacizumab (Avastin®)

Bevacizumab has been used off-label for treatment of nAMD since 2005.
Randomized studies showed that it is an effective therapy for improving vision in nAMD, equal in efficacy and safety to intravitreal ranibizumab and aflibercept in the treatment of nAMD. The main advantage of bevacizumab is the much lower cost of this drug in ophthalmic use. It can be used in Belgium off-label.

1.2 Intravitreal Ranibizumab (Lucentis®)

Ranibizumab has been approved by the European Medicines Agency (EMA) for countries in the EU since January 2007. The approved dose is 0.5 mg of ranibizumab.
It was presumed that ranibizumab would lead to less geographic atrophy, but the RIVAL study could not demonstrate a clinically significant difference between Ranibizumab and Aflibercept.

1.3 Intravitreal Aflibercept (Eylea®)

EMA approval of aflibercept for the treatment of nAMD at a recommended intravitreal dose of 2.0 mg was granted in 2012.
The EU label recommends three initial injections at monthly intervals, followed by eight weekly injections without any subsequent monitoring. However, recent studies indicate that patients might need injections at a shorter interval than every 8 weeks.
The RIVAL study concludes that neither aflibercept nor ranibizumab for nAMD are superior to the other regarding the average visual acuity gains and number of injections during 1 year in a treat-and-extend (TAE) regimen.

A promising approach to improve therapeutic effect and provide sustained disease control could be to increase the dosage of an effective, approved drug. Aflibercept 8 mg is a new formulation at a higher concentration, with improved stability, enabling the intravitreal delivery of a four-times higher molar dose compared with the aflibercept 2 mg formulation. Given the strong binding affinity of aflibercept to VEGF and its estimated intravitreal half-life, the increase in molar dose was projected to allow treatment of patients at intervals of up to 16 weeks after an initial monthly treatment phase.
The findings from PULSAR show that, compared with aflibercept 2 mg, aflibercept 8 mg has the potential to decrease treatment burden in nAMD, while yielding superior anatomic outcomes and similar visual gains. Approximately 80% of patients randomized to receive aflibercept 8 mg maintained their assigned 12-week and 16-week dosing intervals. As aflibercept 2 mg was dosed in a fixed 8 week regimen, we lack data from a head-to-head treat-and-extend study.
Aflibercept HighDose is not reimbursed in Belgium.

1.4 Intravitreal Brolucizumab (Beovu®)

Beovu (brolucizumab) received EMA approval for intravitreal use in patients with nAMD. The brolucizumab phase 3 trials, HAWK and HARRIER, suggested greater durability with similar visual acuity outcomes compared with aflibercept. Fewer injections and comparable visual acuity results remains

attractive for both patients and clinicians.
However, since the beginning of 2020, more reports begin to surface that patients were experiencing severe sterile inflammation that could be difficult to distinguish from infectious endophthalmitis. This brolucizumab-associated inflammation is unusual because it is associated with an occlusive vasculitis and irreversible severe vision loss, albeit rare. Intraocular inflammation is present in 4,6% of patients, retinal vasculitis in 3.3% and retinal vascular occlusion in 2.1%.
This unpredictable severe inflammation could develop weeks after the last brolucizumab injection even if previous injections of brolucizumab were well tolerated, so previous brolucizumab injections without inflammation were no guarantee that subsequent injections would be safe. Post-marketing surveillance and safety committees have been established to investigate and clarify the issue.
Currently, we do not suggest the use of brolucizumab as a first-line treatment. Brolucizumab could have its role as a 3rd (or 4th) line treatment in unresponsive non-monophthalmic nAMD patients. Be aware that close monitoring for signs of inflammation after injection is warranted.

1.5 Intravitreal faricimab (Vabysmo®)

Faricimab has an inhibitory effect on both VEGF-A and Ang-2 and is as such thought to have a longer lasting effect than previous anti-VEGF agents in clinical trials. Anti-VEGF-A inhibits endothelial proliferation, reduces vascular permeability, and suppresses neovascularization. In healthy vessels the angiopoietin-Tie2 signaling pathway helps to regulate angiogenesis and maintain vascular stability. In pathologic conditions such as neovascular AMD, Ang-2 levels are elevated which inhibits Ang-1 signaling and synergizes with upregulated VEGF-A to induce vascular instability via vascular leakage, inflammation and neovascularization. Therefore, a multitargeted approach with simultaneous inhibition of Ang-2 and VEGF-A pathways may result in more durable efficacy through vascular stabilization, improving outcomes beyond VEGF inhibition alone.
BCVA gains from baseline to 2 years are comparable between faricimab and aflibercept. In the TENAYA and LUCERNE trials up to 80% of patients reached a 12w interval (with 45% reaching a 16w interval at year 1 and > 60% at year 2). However, the comparator aflibercept was given at a fix interval of 8 weeks, therefore both trials (TENAYA and LUCERNE) demonstrate non-inferiority but do not allow the evaluation of the proportion of patients that could benefit from a longer aflibercept interval. Retinal vasculitis and vascular occlusions can occur in 0.06 per 10.000 injections.
Faricimab is not reimbursed in Belgium.

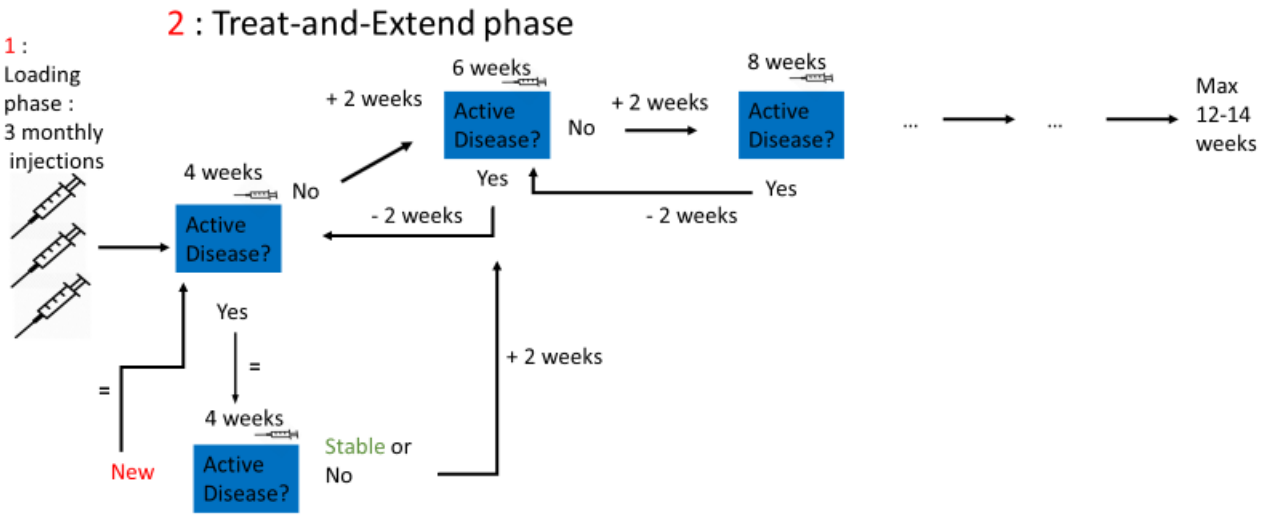
Treatment protocol for anti-VEGF injections

Different treatment protocols have been studied: monthly, Pro Re Nata (PRN), treat-and-extend (TAE), observe-and-extend…
The current recommended treatment protocol consists of a loading phase with 3 monthly injections followed by a treat-and-extend protocol allowing less visits and similar visual outcome compared to a more intensive monthly protocol.
The TAE posology recommends intravitreal injections of anti-VEGF at intervals of four weeks until there is no disease activity. Thereafter, injections are administered at longer and longer intervals, provided there is no recurrence or worsening of disease activity. If there is worsening or recurrence, then the interval is shortened. The presence of new hemorrhage, intraretinal fluid or subretinal fluid is widely used as a surrogate biomarker for disease activity, but persistent fluid with no further morphological

improvement despite continuing injections on three consecutive visits at one monthly interval is regarded as indicative of disease stability.

Practical proposal: Initially, treatment naive patients receive three fixed monthly dosing, and an appointment is normally offered 4 weeks after the third injection for assessment of BCVA and OCT improvement. A fourth injection is administered at this visit and depending on the presence or absence of disease activity, the next review/injection is arranged for 4 or 6 weeks ideally in a one-stop clinic. The one-stop clinic setup is recommended as this ensures that the eye is treated “as is” and disease reactivation is avoided, which may occur with unwarranted additions to the treatment intervals as may result through a two-stop setup.
Provided there are no signs of recurrence clinically or on OCT, the retreatment interval is sequentially increased by 2 weeks each time to a maximum interval of 16 weeks. If there is any sign of recurrence or worsening at any visit, the interval between injections is reduced by 2 weeks, or further back down to 4 weeks, depending on the clinician’s impression of the severity of the recurrence, until disease stability is reached. Once the correct TAE interval is found for the individual patient, apply this interval for 1 year before you rechallenge the TAE interval again, whilst regularly monitoring the patient.
The ALTAIR study also showed that patients extended with 2-week adjustments were more likely than patients receiving 4-week adjustments to maintain 16-week treatment intervals to Week 96. Up to 96.3% of patients in the 2-week extension group who were extended to 16-week treatment intervals during the study were maintained on 16-week intervals to Week 96, compared with 77.6% of patients in the 4-week extension group. So, it is recommended to extend the treatment interval with 2 weeks at a time.

For the comfort of the patient, it is advised to shorten or prolong the interval with 2 weeks at first and then fine-tune the treatment interval by shortening or prolonging with 1 week. The goal is to find the ideal extension interval for the individual patient.
Within a group of patients, every individual has a different TAE interval. But for every individual, once found, the TAE interval is often a constant over time.



New = New hemorrhage / Increase fluid on OCT

Stable = Stable OCT on 2 consecutive visits

The current FDA label for faricimab recommends a loading dose of 4 injections, followed by clinical evaluation 8 and 12 weeks later. Further injection regimens include 1/ weeks 28 en 44, 2/ weeks 24, 36 and 48, or 3/ weeks 20, 28, 36 and 44.
Although additional efficacy was not demonstrated in most patients when faricimab was dosed every 4 weeks, compared to every 8 weeks, some patients may need monthly dosing after the first 4 doses. Patients should be assessed regularly.
Therefore, a practical approach would imply a treat and extend schedule where you extend the interval with 4 weeks for faricimab instead of 2 weeks for the other anti-VEGF agents.

- Can we stop the treatment with intravitreal injections?

The pivotal clinical trials of intravitreal anti-VEGF therapy for nAMD were 2 years in duration. They were not designed to provide evidence on the potential risk of recurrence of disease activity after cessation of anti-VEGF therapy or the impact on visual outcomes of ceasing treatment. Real-world data have provided useful insights.
Analysis of a large real-world dataset of over 2,000 eyes in the Fight Retinal Blindness! registry (receiving intravitreal ranibizumab for nAMD according to a TAE regimen) confirmed a high rate of disease reactivation over time after disease stability had been achieved. Treatment intervals beyond 12 weeks appear to be associated with an increased risk of disease reactivation.
The consensus is that the maximum extension should be 12-16 weeks.
You might consider stopping treatment in selected cases where there are no signs of activity on 3 consecutive 12-week visits. But keep in mind that continuing treatment may help prevent long-term recurrence in eyes with a good response on anti-VEGF treatment. And that the mean VA at first visit after retreatment was lower than that at the beginning of the treatment-free period, demonstrating that VA will not fully recover on resumption of treatment.

- What with bilateral injections?

One in five patients has bilateral active disease that requires bilateral treatment. Treatment for bilateral disease should follow the standard treatment protocols. Treatment responses may be different in the two eyes in patients with bilateral nAMD or nAMD may occur consecutively. This causes

challenges for the planning of a successful TAE regimen. There is no consensus or best clinical practice guidelines for a bilateral TAE approach.
Different options for TAE in bilateral nAMD cases are available:
1. To treat the eyes individually with the aim to synchronize both eyes (eg, treating one eye at 6 weeks and the other at 12 weeks means that a bilateral procedure can be performed every second visit, reducing the overall number of appointments)
2a. To treat both eyes at the same shorter TAE interval
2b. To compromise and treat both eyes at the longer TAE interval (especially if better seeing eye has better stability).
Each option has certain disadvantages. Individual treatment of each eye increases the number of appointments and is less convenient for the patient. If both eyes are treated at the shorter interval of the eye with the shorter TAE timing, the fellow eye will be over-treated. In many cases of bilateral nAMD, one eye may be worse than the other. It might be pragmatic to base visits according to the eye that has better visual potential and longer treatment interval. This approach reduces patient appointments but undertreats the worse eye.
In cases of bilateral nAMD an individual approach for each patient should be discussed and the different solutions should be offered to suit the best interest of the patient.
Performing an injection in both eyes, each injection should be considered a separate procedure with separate povidone-iodine preparation, a new speculum, needle,…

2. Photocoagulation and Photodynamic Therapy (PDT) for neovascular AMD

Laser photocoagulation therapy and verteporfin PDT have shown benefits compared with the natural course in selected subtypes and stages of neovascular AMD. While largely superseded by intravitreal pharmaceutical VEGF inhibition, these two older forms of CNV treatment remain a reasonable therapeutic option for few selected patients.
In the treatment of polypoidal choroidal vasculopathy, PDT can be considered.
The Everest study concluded that after 12 months combination therapy of ranibizumab plus PDT was not only noninferior but also superior to ranibizumab monotherapy in best-corrected visual acuity and superior in complete polyp regression while requiring fewer injections. Combination therapy should be considered for eyes with PCV, when there is no response to loading phase with anti-VEGF.
Recent 2-year results from the Planet study concluded that monotherapy with Aflibercept was noninferior to combination therapy of Aflibercept with rescue PDT. Few patients required rescue PDT, which provided no additional visual benefit.

In non-responders, treatment with PDT or combination therapy (PDT + intravitreal corticoid or intravitreal anti-VEGF) can be considered. However, due to the continuous shortage of Visudyne and the results of the Planet study, it is not recommended. Visudyne is currently reserved for the treatment of chronic central serous chorioretinopathy and choroidal hemangioma.

3. Surgical treatment for hemorrhagic AMD

Subretinal hemorrhage (SRH) is a rare, but devastating complication of nAMD. Damage to overlying photoreceptors has been found to occur within 24 h and degeneration of outer retinal layers within 3 days. The natural history of submacular hemorrhage (SMH) associated with neovascular AMD usually leads to poor VA.
As there is no consensus on the optimal treatment, and data from studies often conflict, no general recommendation can be given for the treatment of hemorrhagic AMD. A classification of submacular

hemorrhage based on size appears practical. Intensive anti-VEGF treatment associated or not with pneumatic replacement may be useful in small hemorrhages, while medium-sized clots may require a surgical approach including vitrectomy. An autologous RPE-choroid graft can be considered in selected cases. Massive hemorrhage has a genuinely unfavorable prognosis. Attention should be given to the fellow eye to prevent active disease, and a hemorrhagic event in the eye that sees better. A surgical approach should be performed within 14-days' duration of submacular hemorrhage.

An autologous RPE-choroid graft or macular surgery can be considered in other selected cases, such as a tear in the retinal pigment epithelium or extensive subretinal fibrosis, that include the fovea. These cases are associated with very poor vision if left untreated and can have a better visual prognosis with surgery.