Graefes Arch Clin Exp Ophthalmol (2011) 249:631–632
DOI 10.1007/s00417-011-1639-3

EDITORIAL

Retreatment criteria in anti-VEGF therapy of exudative AMD: critical analysis of present regimes and new morphological definition of "lesion activity"

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Received: 17 February 2011 / Accepted: 17 February 2011 / Published online: 5 March 2011

In this issue, a series of clinical studies report on different "as needed" anti-vascular endothelial growth factor (VEGF) treatment regimens for exudative age-related macular degeneration (AMD), as they are presently applied in Europe. To date, the only approved VEGF inhibitors for the treatment of eye disease are ranibizumab (Lucentis) and pegabtanib (Macugen).

While visual improvement is frequently achieved following the almost universally accepted 4-weekly triple-injection initiation phase of ranibizumab, the only proven treatment regime to maintain the initial gain in mean visual acuity (VA) is the monthly injection of ranibizumab, as used in the ANCHOR and, MARINA studies [1, 2]. The advantages of this regimen include simplicity and the absence of a need to reconsider the treatment. Disadvantages include an increased risk of endophthalmitis, which can be assumed to be proportional to the number of injections, high expenditure on medication, and perhaps reluctance on the part of the patient to accept such frequent injections.

According to the package insert for ranibizumab in Switzerland, monthly re-injections have priority over an "as needed" regimen. For the countries of the European Union, including Germany, the *summary of product characteristics* (SPC, often called "label" or "package insert") approved by the European Medicines Agency turned out, to the astonishment of most ophthalmologists, to recommend a "PRN" regime constructed on the basis of a retrospectively designed mathematical model, and stating that retreatment should occur only after the patient has experienced a visual acuity loss of 5 letters or more [3]. While it was expected that some type of initiative might be taken to limit the re-injection rate, most experts had expected advantage would be taken of optical coherence tomography (OCT), since this is a commonly available, inexpensive and efficient method of monitoring lesion activity in neovascular AMD. Unfortunately, morphological assessment was given only a secondary role in the management of neovascular AMD.

There is little evidence to support the idea that vision lost to recurrent activity of choroidal neovascularization (CNV) can be fully regained. A predominantly function-driven retreatment concept therefore puts visual function at severe risk. As demonstrated in prospective studies (for example, the SUSTAIN study), the study of Heimes et al. substantiates that we must not allow recurrences to the extent of visual loss, otherwise the initial gain of visual acuity will be lost again within 12 months of starting treatment. It appears that lesion activity associated with acute visual loss is associated with progressive and irreversible photoreceptor damage, even if lesion activity can be suppressed again by renewed anti-VEGF treatment. Consequently, re-treatment should precede visual loss.

The functional outcome of a re-treatment regime based on morphological parameters assessed with SDOCT is reported by Gerding et al., demonstrating the superiority of a morphology-based retreatment regime: when PRN retreatment was initiated at the first signs of exudation (persistent or new sub- or intraretinal fluid on SDOCT), visual improvement was maintained with a slightly increased frequency of injections of 5.8 per year (Gerding et al.) compared to 5 per

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year (Heimes et al.). It was hardly the marginal increase in injection frequency but more likely the use of morphological criteria to define lesion activity that made the difference.

In the same context, Müther et al. showed that delayed initiation of treatment is equally detrimental to the functional outcome, which confirms that macular edema must ideally be avoided or must be responded to before the onset of functional loss. For a subset of patients, a regular pattern of recurrence can be identified and used to set optimal prophylactic re-injection intervals (Hörster et al.).

In summary, reports in this issue and elsewhere [4] demonstrate that in exudative AMD, following initiation of anti-VEGF treatment, morphological changes precede functional changes as indicators of recurrence. Because the available evidence shows that recurrent functional loss is less than fully reversible, a responsible attitude to re-treatment of neovascular AMD must prioritize morphological criteria over functional criteria as they are defined by the European Union Lucentis label. The potential utility of finer functional criteria remains to be elucidated.

It is unknown how many treating physicians actually follow the European SPC in detail. In some countries there is no problem with not doing so, whereas in others it can cause considerable problems with health insurance providers who review the indications for and pre-approve re-treatment. To provide guidance for OCT-based anti-VEGF re-treatment, a group of European experts (see below) assembled in Berlin on 4 June 2010 during the WOC to agree on a uniform concept of intravitreal anti-VEGF disease management in neovascular AMD, based on morphological criteria for individualized re-treatment. The algorithm below is based on assessment of activity every 4 weeks using SDOCT:

1. Relevant diagnostic procedures
   a. Fundoscopy
   b. Fluorescein angiography (primarily for initial diagnosis)
   c. Transfoveal OCT
   d. Best-corrected visual acuity (BCVA)
2. Initial treatment phase (CNV with classic component, active occult CNV, retinal angiomatous proliferation)
   a. Three injections at intervals of 4 weeks beginning without undue delay
   b. Assessment of lesion activity 4 weeks after third injection (see 3a)
   c. i. If activity as per 3b→2a
      ii. If absence of activity as per 3c→3a
3. Maintenance phase
   a. Assessment of activity every 4 weeks
      i. Fundoscopy
      ii. Transfoveal OCT, preferably with fundus photograph
      iii. BCVA
      iv. Fluorescein angiography (optional, rarely necessary)
   b. Criteria for re-treatment (one or more of the following):
      i. Intraretinal cystoid oedema
      ii. Subretinal fluid
      iii. Diffuse thickening of the fovea
      iv. Expanding serous pigment epithelial detachment (PED)
      v. New sub- or intraretinal hemorrhage
      vi. BCVA loss attributable to other signs of lesion activity
   c. Criteria for temporarily withholding treatment:
      i. Absence of criteria as per 3 b or
      ii. Stable serous PED or
      iiI Stable intraretinal fluid or cystoid spaces that have not responded to three initial injections
   d. Criteria for considering cessation of treatment
      i. Untreated observation for half a year or more without lesion activity
      ii. Visual acuity 0.05 or worse without chance of improvement

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