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Perspective

Optimizing the Anti-VEGF Treatment Strategy for Neovascular Age-Related Macular Degeneration: From Clinical Trials to Real-Life Requirements

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This Perspective discusses the pertinence of variable dosing regimens with anti-vascular endothelial growth factor (VEGF) for neovascular age-related macular degeneration (nAMD) with regard to real-life requirements. After the initial pivotal trials of anti-VEGF therapy, the variable dosing regimens pro re nata (PRN), Treat-and-Extend, and Observe-and-Plan, a recently introduced regimen, aimed to optimize the anti-VEGF treatment strategy for nAMD. The PRN regimen showed good visual results but requires monthly monitoring visits and can therefore be difficult to implement. Moreover, application of the PRN regimen revealed inferior results in real-life circumstances due to problems with resource allocation. The Treat-and-Extend regimen uses an interval based approach and has become widely accepted for its ease of preplanning and the reduced number of office visits required. The parallel development of the Observe-and-Plan regimen demonstrated that the future need for retreatment (interval) could be reliably predicted. Studies investigating the observe-and-plan regimen also showed that this could be used in individualized fixed treatment plans, allowing for dramatically reduced clinical burden and good outcomes, thus meeting the real life requirements. This progressive development of variable dosing regimens is a response to the real-life circumstances of limited human, technical, and financial resources. This includes an individualized treatment approach, optimization of the number of retreatments, a minimal number of monitoring visits, and ease of planning ahead. The Observe-and-Plan regimen achieves this goal with good functional results.

Translational Relevance: This perspective reviews the process from the pivotal clinical trials to the development of treatment regimens which are adjusted to real life requirements. The article discusses this translational process which– although not the classical interpretation of translation from fundamental to clinical research, but a subsequent process after the pivotal clinical trials – represents an important translational step from the clinical proof of efficacy to optimization in terms of patients' and clinics' needs. The related scientific procedure includes the exploration of the concept, evaluation of security, and finally proof of efficacy.

Perspective

Major scientific advancements have recently been made in the management of age-related macular degeneration (AMD), one of the most frequent macular pathologies, and AMD has been the focus of numerous genetic, histologic, pathogenic, ocular imaging, and therapeutic studies. One of the major breakthroughs in the management of AMD was the introduction of antivascular endothelial growth factor (anti-VEGF) treatment for neovascular AMD (nAMD). The pivotal trials, the "Minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration"[1] and the "Anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in age-related macular degeneration"[1] were two multicenter, randomized, controlled, phase

3 clinical trials in which the efficacy of monthly intravitreal injections of the anti-VEGF ranibizumab was shown to significantly improve visual acuity (VA) compared with sham treatment[2] or photodynamic therapy[3] in patients with nAMD. This overwhelming improvement in the prognosis of nAMD was achieved on the basis of monthly injections. However, this high treatment frequency placed a heavy burden on the management of patients with chronic nAMD, thereby requiring many clinical and therapeutic interventions over the course of the patient's lifespan due to the repetitive treatment scheme and the inability to "cure" the disease.[4] In addition, the incidence of nAMD is growing, and the increase in life expectancy is expected to contribute further to this problem.

Soon after the introduction of anti-VEGF treatment for nAMD, alternative retreatment regimens were explored in order to reduce the treatment burden. The earliest approach, a fixed reduction to injections of ranibizumab every 3 months, resulted in the loss of initial VA improvement and was shown to be significantly inferior to monthly injections, although a subset of patients did well on this regimen.[5–7] Several years later, the phase 3 trial "VEGF trap-eye: investigation of efficacy and safety in wet AMD" (VIEW) with aflibercept, a VEGF decoy receptor, investigated the outcome of bimonthly versus monthly fixed retreatment schedule and found functional noninferiority at 1 year.[8] However, the fluctuating retinal thickness in the bimonthly regimen suggested that this might be suboptimal for a significant proportion of eyes. Thus, any fixed regimen does not appropriately take into account the high variability of treatment need between individuals, therefore resulting in overtreatment in patients with low treatment need or undertreatment in patients with high treatment need.

AMD is a highly variable disorder with a large spectrum of pathogenic factors, genetic backgrounds, phenotypic features, and therapeutic responses. Although the reasons are still poorly understood, patients with nAMD show high interindividual variability in the need for anti-VEGF injections. This became evident in the pro re nata (PRN) regimen, the first individualized treatment regimen.[9–12] In this regimen, the need for retreatment is determined at monthly assessment visits, allowing for a reduced number of injections. This individualized regimen was the first to be widely adopted in clinical practice. However, monthly monitoring visits are still required to detect early disease recurrence.

While effective, monthly visits are in reality a heavy burden on patients and institutions. Indeed, these monitoring visits are the most time- and resource-consuming part of patient care with anti-VEGF therapy for individuals with nAMD. The number of monitoring visits in turn determines the requirement for human resources (doctors and technicians), machines (optical coherence tomography [OCT]), and examination space, and these resources are often limited. In addition to the institution's limitations, the patients' compliance may be lacking for monthly monitoring visits. A further downside of the PRN regimen is the constant uncertainty as to whether a patient will need an injection, which can cause logistic problems for the work flow around the injections. Not surprisingly, recently published real-life data revealed poor functional results,[13,14] probably due to general undertreatment as shown by the low mean number of injections and the less-than-monthly visits. This may be a consequence of the aforementioned problems with logistical issues and limited resources.

These problems have been addressed by the Treat-and-Extend regimen, which has become the most commonly used regimen in the United States, and is becoming increasingly popular internationally. The cornerstone of the regimen is the progressive lengthening of the intervals between the visit-injection dates: Each visit is combined with an injection, and the visit result determines the subsequent interval to the next visit-injection date. This approach allowed for reducing the number of injections and simultaneously the number of visits. Several reports from 2009 onwards have shown that overall good VA outcomes may be achieved with fewer patient visits and injections along with lower costs compared with fixed, monthly retreatment.[15–17] In comparison with the PRN regimen, the Treat-and-Extend regimen showed several advantages: The number of visits was reduced along with the number of injections, ranging from 7.6 to 8.4 in the first year.[15–17] The injections are administered at each visit, thereby facilitating the planning ahead, however, requiring a one-stop clinic allowing for same day visits and injections. In addition, several authors have speculated about a favorable effect of fewer exudative recurrences with minimized structural damage.

In 2008, during our early experience with PRN, and before the introduction of the Treat-and-Extend regimen, our group began to develop a different treatment algorithm. It started with the clinical observation of a relatively stable intra-individual need for retreatment. Based on our experience of

the challenges of PRN retreatment, we speculated that it may be possible to combine the advantages of PRN (minimum number of injections) with the advantages of a fixed regimen (skipping time-consuming visits and planning the injections ahead) if we could determine the optimal treatment interval for each individual patient, and if this interval was relatively stable over time. Thus, we aimed to develop such a regimen, which would ultimately alleviate the burden of nAMD care.

In the first step, we performed a pilot study that investigated the regularity of the individual retreatment need.[18] We examined the ability to predict future need of retreatment on the basis of past experience with a given individual. In this pilot study, 39 patients agreed to undergo frequent visits. After the initial three loading doses of ranibizumab every month, patients were seen at weeks 4, 5, 6, 7, 8, 10, 12, 14, and 16 and then monthly after each injection, until signs of recurrence were identified on spectral domain OCT, followed by prompt re-injection. The intensified visit schedule served to increase the precision of the recurrence time point. The study duration from months 3 to 15 allowed for statistical analysis of intra-individual consecutive treatment intervals of up to 14 weeks. The results revealed that the intra-individual standard deviation of the intervals was limited to 0 to 2 weeks, with the first interval being predictive of 70% of the variance of the following intervals.[18]

On the basis of such regular rhythms and predictability of retreatment need, our subsequent study proposed to take advantage of this in a new regimen, called Observe-and-Plan, and to validate this regimen by determining its functional outcomes.[19] The concept of this regimen was to first measure and then plan the individual ideal retreatment interval. This interval is then applied for several fixed injections without intermittent evaluation. Monitoring visits after each series of injections allow for adjustment of the interval in the subsequent injection series. Thus, the advantages of the individualization (optimal number of injections) and of the fixed regimen (reduced number of assessment visits and planning ahead) would be combined. More precisely, after the initial three loading doses, the patient was followed in a monthly rhythm until signs of recurrence were observed on SD-OCT (i.e., the Observation period). As this injection-recurrence interval was considered slightly too long for optimal treatment, the ideal treatment interval was considered to be 2 weeks shorter (as there was no sign of recurrence at the previous month). This was the interval that was subsequently applied in the individually fixed treatment plan for several injections without monitoring visit (i.e., the Plan period).[19] However, gradual changes in the need for retreatment may occur over time. Therefore, readjustment visits were required after an injection series, with identical intervals from the last injection, at the latest after 6 months, and/or after three injections. The interval of the subsequent treatment plan was adjusted by steps of 2 weeks, depending on presence or absence of fluid on spectral domain OCT.[19] A dry macula would justify longer intervals for the next injection series, and fluid on OCT would prompt shortening of the interval. The possible treatment plans were: three injections at 1-, 1.5-, or 2-month intervals or two injections at 2.5- or 3-month intervals. Planned treatment intervals longer than 3 months were not allowed because of the absence of sufficient data about the stability over time. When the macula remained dry after a 3-month interval, the subsequent step was observation every 1.5 to 2 months. Figure 1 shows the sequence of treatment plans according to the protocol. As an example, a patient may be monitored monthly after the initial three loading doses, then show first signs of recurrence on OCT at 3 months after the last loading dose. As the macula was dry at 2 months but not at 3 months, the probably best treatment interval was considered to be 2.5 months. Thus, the patient would immediately proceed to his fourth injections, followed by a fifth injection without monitoring visit 2.5 months later. Further 2.5 months later (equivalent to 5 months $= 2 \times 2.5$ months after the last monitoring visit), the patient would then be clinically assessed including an OCT, in order to adjust the next injection intervals to either 2 months (series of three injections) in case of fluid present on OCT, or extend to 3 months (series of two injections) in case of a dry macula, followed by a new assessment visit after a total of 6 months since the previous assessment visit, and so on.

The aims of the 2-year study with this Observe-and-Plan regimen were to validate the regimen based on functional outcomes and to describe the degree to which the number of injections and visits could be reduced.[19,20] Although this was not a comparative study, it was able to show that the Observe-and-Plan regimen allowed for maintaining the initial visual benefit over 2 years. While the initial VA improvement is mostly dependent on the tissue potential to recover function under VEGF suppression, the retreatment strategy is the main factor for best

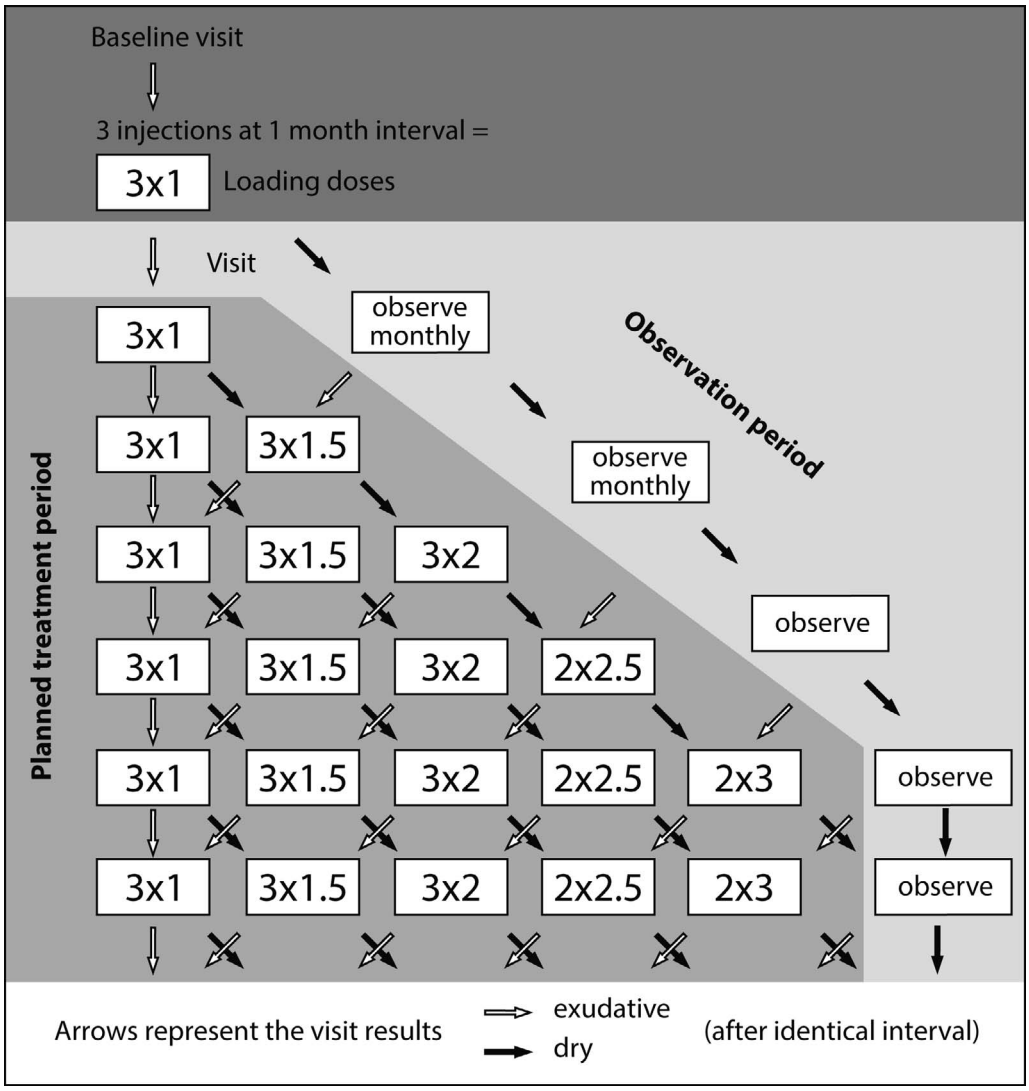

Figure 1. Observe-and-Plan regimen with anti-VEGF for neovascular age-related macular degeneration. An overview of the phases (loading period, observation period, and planned treatment period) and the typical sequence of consecutive treatment plans are shown.

possible maintenance of this initial benefit over time. Thus, the excellent and stable functional results over 2 years using the Observe-and-Plan regimen served as clinical validation of the regimen.[20]

Although functional validation of the regimen is essential, the main interest of the Observe-and-Plan regimen was to achieve these results with fewer visits and an individualized number of injections, which are the main factors impacting the clinical burden: We found that a mean of four visits after baseline was needed during the first year, and this was reduced further to 2.9 visits during the second year. The mean numbers of injections were 7.8 in the first year (including loading doses) and 5.8 in the second year, which were quite similar to other variable-dosing regimens (Fig. 2).[9,12,15,20] However, the number of visits was three to four times less than what would be needed in PRN with monthly visits[9] and less than half of what is needed in the Treat-and-Extend regimen (Fig. 2).[15]

The main benefit of the Observe-and-Plan regimen is related to the dramatically lower number of ophthalmic monitoring visits; because these visits are the most time- and resource-consuming part of patient care in individuals with nAMD. The number of visits determines the institution's capacity to cope with the burden of nAMD. Thus, the Observe-and-Plan regimen enables institutions to care for multiple patients with nAMD using the same available resources as compared to PRN or Treat-and-Extend.

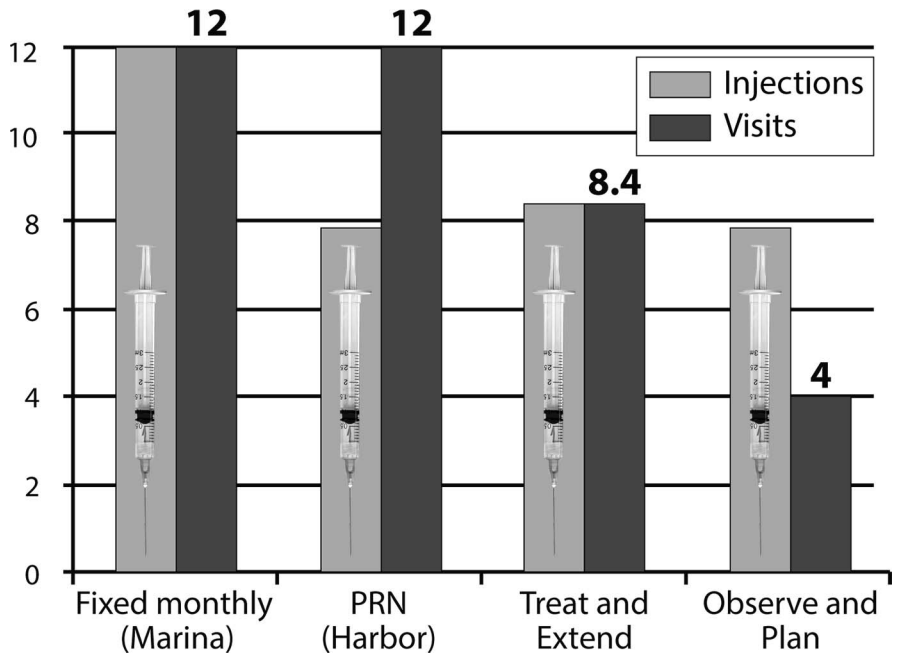

Figure 2. Comparison of injection and visit numbers for different retreatment regimens.

Second, the regimen offers the ability to plan ahead for several injections up to 6 months. And third, it is suitable for both 1-stop and 2-stop clinics: Most of the injections are planned ahead and predominantly without an associated visit, which is well compatible with both types of clinics. Based on these advantages, this regimen offers an interesting tool to achieve optimal patient care within the given real-life limitations of restricted resources. In addition, the regimen may improve patients' compliance: Patients usually appreciate not only fewer appointments, less time spent in clinic, but also the planning ahead for several months. Hopefully, the increased application of this Observe-and-Plan regimen will improve the real-life functional results of anti-VEGF treatment for nAMD in the future.

The economic impact of the Observe-and-Plan regimen in terms of direct medical cost is similar to the PRN and Treat-and-Extend regimen.[19] This is not surprising as the direct medical cost is determined mainly by the number of injections. However, indirect cost may be greatly influenced by the number of visits, as discussed before.

A few challenges of the Observe-and-Plan regimen should be mentioned. First, as we reported for the initial 2-year results, late recurrences after more than 3 months of observations may be aggressive and may sometimes necessitate dramatic shortening of the treatment interval.[20] We therefore recommend careful evaluation and clinical judgment in cases of late recurrence. Second, establishing the treatment plan with several dates and precise intervals requires well-organized communication and calculation of the correct timing. This can be greatly facilitated if clinics can integrate an informatics tool that will calculate the treatment windows. Third, management of patients with bilateral nAMD may require some additional considerations on how to harmonize the treatment and follow-up dates for the two eyes. In our experience, the need for retreatment is often amazingly parallel. If not, it is helpful to slightly modify the by-protocol intervals. Minor interval adjustments or application of a slightly different number of retreatments may help to establish a harmonized treatment for both eyes (for example 4×1.25 and 2×2.5 months). It is usually possible to find a solution in which one eye receives injections every second or third time that the other eye is injected. Thus, the benefit of the regimen can be maintained, even in patients with bilateral nAMD.

In conclusion, the development of the Observe-and-Plan regimen illustrates a scientific process subsequent to the phase 3 clinical trials. During this process, the efficacy target set by the clinical trials was translated into a treatment approach that takes into account real-life requirements and challenges. In comparison with the initially proposed fixed monthly regimen of anti-VEGF injections for nAMD, the

earliest variable-dosing regimen (PRN), which reduced the number of injections, and the subsequent introduction of the Treat-and-Extend regimen yielded a better planning-ahead protocol and reduced the number of visits. Finally, the Observe-and-Plan regimen was able to achieve good functional outcomes with dramatically reduced numbers of visits and a number of injections, as required by the pathology of the individual patient. This was obtained by individualized prediction of the need for retreatment. Because fewer visits are needed, and due to the additional advantage of the ease of preplanning of the injections, the development of this regimen enabled the optimization of human and technical resources. The Observe-and-Plan regimen can alleviate the clinical burden of anti-VEGF treatment for patients with nAMD, thereby improving the institutional capacity for chronic care management of this disorder.

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