The hallmark feature of the wet or neovascular form of age related macular degeneration (nvAMD) is the presence of choroidal (or retinal) neovascularization (CNV). If left untreated, CNV may result in significant central vision loss due to complications including exudation, leakage and ultimately subretinal fibrosis causing remarkable photoreceptor loss. While the mechanism of development is not fully understood, the process of neovascularization is driven by upregulation of angiogenic cytokines, principally vascular endothelial growth factor (VEGF). Inhibition of VEGF with intravitreal anti-VEGF therapy has become the standard of care for macular CNV, helping to prevent legal blindness in millions of affected patients worldwide.

The Food and Drug Administration (FDA) drug approval process is designed to ensure that a new treatment is both safe and efficacious when compared to previous therapies or observation. FDA registration trials are generally designed with a regimented protocol that maximizes potential efficacy. The first intravitreal anti-VEGF drug approved by the FDA for neovascular AMD was pegaptanib sodium injection (Macugen) that was dosed every 6 weeks in the pivotal, registration trials (VISION Trials\(^1\)). Subsequently, in the ranibizumab (MARINA and ANCHOR\(^2\)) and aflibercept\(^3\) (VIEW 1 & 2\(^4\)) pivotal registration trials for nvAMD, dosing these drugs every 4 weeks (q4W) was associated with unprecedented rapid and consistent vision gains in eyes with nvAMD. In addition to q4W dosing arms, the aflibercept trials included aflibercept groups treated every 8 weeks (q8W) after three q4W injections, that ‘on average’, demonstrated vision gains comparable to the q4W therapy groups. In year 2 of the aflibercept trials, patients were treated at least every 12 weeks with additional treatments given “as needed” based on q4W study visits.\(^5\)

Occasionally, off-label treatment with a drug that is FDA approved for one disease is found to be efficacious for a non-FDA approved indication. This was the case with bevacizumab, a chemotherapy approved for certain solid malignancies, that was then shown to have safety and efficacy outcomes similar to ranibizumab in comparative effectiveness trials in patients with nvAMD.\(^6\) Bevacizumab has yet to be tested against aflibercept in a similar manner. Patients are often started on bevacizumab due to significant cost difference between these drugs and visual benefit when dosed similarly to ranibizumab or aflibercept.\(^7\) However, issues with compounding pharmacies regarding bevacizumab may limit its use in some cases.\(^8,9\) These issues include concern over sterility, shelf-life of compounded injectables, and silicone oil droplets in pre-filled syringes.

Once a drug has received FDA approval, or has been shown to have safety and efficacy as an off-label therapy, clinical experience may result in dosing regimens that differ from those used in registration trials. Typically, in registration trials, only one eye receives treatment with
the study drug, and trials often mandate regimented dosing for 1 to 2 years.\textsuperscript{2-4} Thus, these clinical trials give limited information regarding appropriate long-term dosing for a chronic and often bilateral disease like nvAMD. Many patients in “real-world” clinic settings are different from patients enrolled in clinical trials. They may present with more advanced disease with poor visual acuity or they may demonstrate clinical findings (e.g. retinal pigment epithelial tears, eccentric non-foveal CNV, or large subretinal hemorrhages) that were exclusion criteria for these studies. Often AMD patients are limited by debilitating medical and/or social issues and returning on a q4W, or even q8W, schedule may be prohibitive. Clinical trials such as the Comparison of AMD Treatments Trials (CATT) and A Study of Ranibizumab Administered Monthly or on an As-needed Basis in Patients With Subfoveal Neovascular Age-related Macular Degeneration (HARBOR\textsuperscript{10}) demonstrated that the need for retreatment to control CNV-related exudation is highly variable between different patients, but is often consistent in one eye of an individual patient. However, it is important to note that nearly every study in which eyes were treated less often than q4W (ranibizumab and bevacizumab) or less often than q8w following three q4W (afibercept) have failed to demonstrate long-term maintenance of initial vision gains.\textsuperscript{11} Therefore, undertreatment may be one of the causes of long term visual acuity loss in the maintenance of nvCNV\textsuperscript{12} although other causes of long-term decay such as atrophy\textsuperscript{12} and fibrosis should be considered.

In any medical decision, best clinical practice is guided by the underlying goal of minimizing risk and treatment burden while maintaining maximum benefit. The ocular risks of intraocular injection, most notably endophthalmitis, are low, but complications can rarely occur. The reported risk of endophthalmitis following an intravitreal anti-VEGF injection varies, with recent studies showing rates of 0.02%-0.09%.\textsuperscript{14} This small risk, combined with some lingering concerns regarding the potential for systemic risks (e.g. thromboembolic event) of long-term intravitreal anti-VEGF therapy, should be weighed against the risk of vision loss from under-treatment.\textsuperscript{15-17}

With nvAMD, most retina specialists rely on findings from clinical examination and optical coherence tomography (OCT)) to determine if a treatment regimen is adequate in controlling disease activity. Analogous to oncology, the goal is to maintain disease remission while minimizing side effects and treatment burden. The pro re nata (PRN) or “as-needed” arm in the CATT clinical trial required monthly evaluation but withheld retreatment until there was recurrence of disease activity; however, it failed to preserve vision gains comparable to monthly therapy.\textsuperscript{18} Moreover continued monthly evaluation (with or without injection) may not be feasible for real world patients. Furthermore, while patients in clinical trials could be seen, and treated within a window around a scheduled 4-week visit, insurance providers may deny reimbursement for treatments performed prior to 28 days following the last treatment. These limitations may make it difficult to follow the type of PRN regimens used in clinical trials. Appropriate management of nvAMD in patients with particularly aggressive disease may require injections at intervals shorter than Q 4 weeks.\textsuperscript{19,20}

Given their impression that PRN dosing may not provide optimal visual acuity outcomes and given their desire to minimize treatment burden, many retina specialists favor a “treat-and-extend” regimen (TER) when managing nvAMD with intravitreal anti-VEGF therapy. In the 2015 Preferences and Trends (PAT) survey of the 2600 members of the American Society of Retina Specialists (ASRS), 64.8% of US respondents and 42.1% of international respondents reported
that the TER was their preferred approach for management of active nvAMD. While injection intervals vary in TER among retina specialists, most will begin with monthly treatment until a “maximal response” (defined as no further anatomic and/or visual improvement) is achieved. Once a maximal response is attained, treatment continues, but with an attempt to gradually extend the interval between visits and retreatments by 1-2 weeks based upon clinical examination and OCT findings. However, the upper limit of interval between visits may vary among clinicians at 2 to 4 months (with 3 months the most common upper limit). If leakage is observed on the extension of a follow-up interval, the interval is shortened until maximal response is achieved again. Thus, the goal of the TER is to establish an individual patient’s optimal treatment interval since many eyes will show a predictable pattern of disease recurrence. While some patients (approximately 10-20%) may demonstrate extended disease quiescence after initial remission which allows for long intervals of 10-12 weeks between treatments, others (approximately 10-20%) may continue to need monthly treatment due to persistent disease activity. In some patients it may not be possible to predict recurrence, and some retina specialists will therefore examine patients (without injecting) in between injection visits in an effort to avoid unnecessary injections especially in eyes with ostensibly quiescent disease.

Now, more than ever, we realize that nvAMD is a chronic disease. Many retina specialists have patients who continue to need treatment despite 10 years or longer of anti-VEGF therapy. As clinicians gain experience with intravitreal anti-VEGF therapy they may choose to individualize their treatment regimen based on prior experience. For example, in an eye considered to be at low risk for recurrent hemorrhage and permanent vision loss, one could select a PRN regimen, with a plan to switch to a TER if there are early or frequent recurrences of exudation.

As the goal of most anti-VEGF regimens is to maintain remission of disease activity, some retinal specialists may consider switching anti-VEGF agents in eyes that cannot be controlled with q4W therapy or cannot be extended beyond q4W dosing. From the analyses of OCT data in CATT and the aflibercept pivotal trials (VIEW 1 and 2), aflibercept was slightly superior to ranibizumab and bevacizumab in reducing retinal thickness, and both aflibercept and ranibizumab were more effective in reducing retinal thickness versus bevacizumab. However, in CATT, up to 40% of eyes demonstrated disease remission on OCT with monthly bevacizumab injections.

The ultimate decision regarding injection frequency and drug selection will be based upon a combination of clinical examination and OCT findings, good clinical judgement, and patient input regarding distance needed to travel, need for a ride, and their willingness to be seen frequently with or without injections at each visit. As current evidence suggests continuous fixed treatment regimens are associated with the best visual outcomes and patients who have poor vision in the fellow eye might best benefit from these regimens in terms of maximizing their chance for maintaining an independent lifestyle. Some patients who maintain good vision in both eyes may be willing to accept a possible increased risk of vision loss in return for the reduced treatment burden offered by TERs.

Patients with unilateral nvAMD have a high risk of neovascular conversion in their fellow eye. New or recurrent CNV is also likely to occur in eyes with previously treated CNV. For these reasons, most retina specialists recommend regular dilated funduscopic examination with
diagnostic imaging of both eyes in patients with nvAMD. The frequency of examinations in patients at risk for nvAMD should be determined by the treating physician based on patient-specific factors. The determination of appropriate follow-up interval may be influenced by factors such as visual acuity, clinical appearance, family history, symptoms, imaging findings, and the status of the fellow eye.

Tremendous advances in our understanding of at least some of the factors leading to nvAMD, coupled with the development of highly efficacious therapeutic agents have dramatically improved our ability to manage patients with nvAMD. The wealth of data generated by large, randomized clinical trials has helped to guide clinicians in such management. However, equally apparent from this data and coupled with real-world experiences is that while many patients respond similarly, many do not, and one set algorithmic approach to these patients is not possible. Each patient requires careful evaluation and follow-up, and may require modifications in the choice of therapeutic agent and dosing regimen, occasionally even from one eye to the other. A tailored approach to patients often yields the most fulfilling outcome.

References


