Finding the optimal treatment plan for exudative AMD: a review of current anti-VEGF dosing regimens

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ABSTRACT

Age-related macular degeneration is the leading cause of severe central visual acuity loss in people over 50 years of age. Macular degeneration is a complex spectrum of normal age-related changes including reduced photoreceptor density, ultrastructural changes in the pigment epithelium, formation of lipofuscin granules, accumulation of basal laminar lipid-rich deposits, and progressive changes in the choriocapillaris. These changes may cause disturbances in Bruch's membrane allowing vessels originating from the choriocapillaries to form a new and abnormal fibrovascular complex which is the hallmark of exudative AMD.[1,2]

It is well-established that vascular endothelial growth factor (VEGF), plays a major role in the neovascular or exudative form of AMD, by aiding in the induction of angiogenesis and enhancing vascular permeability.[3,4] Consequently, Intravitreal injections with medications targeting VEGF have become the standard of care for exudative AMD. Currently there are several anti-VEGF drugs that are used in the treatment of exudative AMD: bevacizumab (Avastin), ranibizumab (Lucentis), and VEGF Trap (Eylea).

While Intravitreal anti-VEGF treatments successfully work to stabilize and even improve vision in patients with exudative macular degeneration, controversy still remains regarding the optimal treatment plan for patients. The question of how frequently to treat patients is important as many practitioners and patients alike recognize the burden of monthly injections. This paper seeks to review the data for current anti-VEGF treatment regimens in order to help elucidate the optimal treatment plan to maximize visual outcome and minimize burden to the patient and healthcare system.

Key words: exudative AMD, anti-VEGF, intravitreal injections.

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ANTI-VEGF DOSING REGIMENTS: REVIEW OF THE PERTINENT STUDIES

The MARINA and ANCHOR trials, on which current treatment of exudative AMD is based, used traditional monthly treatment regimens. Since these landmark trials, physicians have tried several different treatment regimens in order to determine the optimal treatment plan for patients with exudative AMD. These alternative dosing regimens include a quarterly where injections are given every 3 months: a prn regimen where retreatment is given only in the

case of recurrent retinal bleeding or fluid accumulation, and a treat and extend where treatment intervals are sequentially lengthened until signs of choroidal neovascularization recur.

A. Quarterly treatment regimens

Initial studies looking at alterations in the fixed monthly schedule investigated quarterly protocols. The Phase IIIb multicenter randomized double-masked sham injection controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal CNV with or without classic CNV secondary to AMD (PIER study) was one such study. During this study, patients received ranibizumab injections monthly for 3 months and then once every 3 months for 2 years. The study showed that treatment effect declined in the ranibizumab groups during quarterly dosing. Specifically, after 3 months of monthly injections, there had been a mean gain of 2.9 and 4.3 letters for the 0.3mg and 0.5mg doses, respectively, but at months (after having transitioned to every 3 month injections) the mean change in visual acuity overall was -1.6 and -0.2 letters. Thus the initial improvement gained at month 3 was lost by month 12 but there was overall stabilization of visual acuity.[5] The efficacy and safety of ranibizumab in patients with subfoveal CNV secondary to AMD trial (EXCITE) similarly showed a less favorable outcome when the fixed monthly schedule was altered. After 3 initial monthly injections, patients were given either monthly ranibizumab injections or quarterly treatments. The study showed that both treatments maintained best corrected visual acuity in patients with CNV secondary to AMD however, at month 12, visual acuity gain in patients with the monthly regimen was higher than that of patients receiving the quarterly regimen.[6]

The Safety Assessment of Intravitreal Lucentis for AMD (SAILOR) study, showed visual acuity did not improve as significantly in patients treated with quarterly regimen. In this study, 4300 patients received 0.3mg or 0.5 mg of ranibizumab every 3 months after the initial series of three monthly injections. After the first 3 injections the mean visual acuity improved 5.8-7.0 letters but by study end at months the visual gain was only 0.5-2.3 letters with an average of 3.9-4.6 treatments over 8.8 visits at 1 year.[7] All three of these trials showed the visual gain in patients receiving quarterly treatments was less than those receiving monthly treatments. While the quarterly regimen did succeed in maintaining visual acuity in these patients, these trials suggest quarterly monitoring may not be sufficient to monitor and capture disease progression in some patients.

B. Prn or as needed treatment regimens

Pro re nata (prn), or as needed, treatment regimens have been evaluated in several trials. The Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) trial evaluated the use of prn dosing with ranibizumab. The trial enrolled 40 patients in a two-year trial treated with 3 consecutive monthly injections of 0.5mg of ranibizumab followed by monthly evaluation and retreatment. Retreatment was based on an increase in OCT central retinal thickness of at least 100 microns or loss of BCVA of 5 letters or more on the EDTRS chart. During the second year these criteria for retreatment also included a qualitative increase in fluid on OCT. The trial showed favorable outcomes with 37 total patients gaining on average 10.7 letters over two years with an average of 9.9 injections in this time, including the initial series of 3 injections. Of note, a wide range of injections was necessary to maintain improved or stable vision with some patients requiring only the minimum of 3 injections and 2 of the patients requiring the maximum of 24 injections.[8]

The Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular AMD: SUSTAIN study looked at prn dosing in patients with subfoveal CNV secondary to AMD. Five hundred thirteen patients received a series of 3 monthly injections and then were followed monthly and treated based on visual acuity decrease by more than 5 letters or increase in central retinal thickness by greater than 100 microns. Overall visual acuity declined slightly at month 8 but by 12 months there was a mean improvement of 3.6 letters by 12 months. Additionally patients received on average 2.7 retreatments after the initial loading series of 3.[9] The study results, while not as monthly injection trials, show that a prn treatment regimen can achieve acceptable patient outcomes.

The Comparison of AMD Treatment Trials, or CATT enrolled 1208 patients treated with bevacizumab or ranibizumab according to monthly fixed dosing or prn dosing regimens. At one year, there was no significant difference in visual acuity outcomes in the ranibizumab monthly dosing

and as needed dosing arms and the same comparison for bevacizumab dosing was inconclusive.[10] At 2 years 60% or more of patients in all groups had 20/40 vision or better. There were subtle differences detected at two years between the two dosing regimens with as needed dosing producing 2.4 letters less mean gain in visual acuity compared to monthly dosing.[9] Of note, patients in the as needed arm of this trial did not receive a series of three loading doses as in other studies noted above. The IVAN or Inhibit VEGF in Age-related CNV randomized trial was performed in the UK with 610 participants. This trial showed as needed treatment was equivalent to monthly treatment at one year with the as needed group receiving a series of three loading injections before receiving as needed treatments. At two years the treatment regimen comparison was inconclusive in IVAN.[11]

Overall, these studies show evidence that individualized treatment, when used in combination with frequent follow-up is a viable alternative to the traditional fixed monthly treatments used in the ANCHOR and MARINA trials. While visual acuity results were favorable and the number of total injections decreased compared to a fixed monthly regimen, the total burden of visits does not change with this approach.

C. Treat and extend treatment regimens

Currently, no prospective studies have been performed comparing the treat and extend dosing regimen to either a monthly or as needed regimen. A retrospective case series of 92 patients followed for 2 years shows overall positive results for the treat and extend regimen. In this study patients were treated monthly until there was no intraretinal or subretinal fluid on OCT, then the treatment interval was subsequently extended by two week intervals. Over one year, 96% of patients lost fewer than 3 lines and 32% of patients gained 3 or more lines of vision. The mean number of injections over 1 year was 8.3. The study concluded that eyes with exudative AMD showed overall improvement with a treat and extend regimen.[12]

Oubraham et al. published a retrospective study comparing the treat and extend regimen to a prn treatment regimen. In their study 38 patients were treated according to a treat and extend regimen and 52 patients with a prn regimen. At 1 year the mean visual acuity was greater in the treat and extend group with a mean gain of 10.8 letters compared to a mean gain of 2.3 letters in the prn group. The treat and extend group received more injections with an average of 7.8 injections per patient compared to only 5.2 injections with the as needed treatment group. Each group had a similar number of follow-up visits with an average of 8.5 visits in the treat and extend group and 8.8 visits in the prn group.[13] The treat and extend protocol showed more flavorable visual acuity outcomes while still being able to reduce the number of visits and injections.

The one-year results of the Lucentis Compared to Avastin Study (LUCAS) first randomised, double blind non-inferiority trial using the treat and extend protocol for both ranibizumab and bevacizumab in the treatment of neovascular AMD were recently published. This trial enrolled 441 patients who received monthly injections of ranibizumab and bevacizumab until inactive disease was achieved and then treatment periods were extended by 2 weeks at a time up to a maximum of 12 weeks. The improvement in visual acuity in both treatment groups, ranibizumab and bevacizumab, using the treat and extend protocol was comparable to visual acuity results in the monthly treatment groups of the CATT trial.[14]

COMPARING THE STRATEGIES

Most providers do not strictly adhere to one predetermined method when treating their patients with exudative macular degeneration. Rather, treatment plans are individualised to the patient's individual needs. The majority of retina specialists continue to use an initiation phase, usually a series of three monthly injections, however beyond this they may follow patients monthly and treat if there are signs of exudation (similar to a prn strategy), use a treat and extend method, or a combination of both. In a survey of retina specialists by the American Society of Retina Specialists, 17% reported they still adhere to a monthly regimen, 43% used an as needed, or prn, dosing regimen, and 34% reported they treat and extend.[15] The 2014 survey by ASRS showed a significant change in these trends with only 2% of providers treating with a monthly regimen, 16% with a prn regimen, and an increase to 78% of providers treating with a treat and extend protocol.[16]

While monthly injections seem to be the most definitive method for achieving favourable visual acuity outcomes in

patients with exudative AMD, a regimented approach such as this is impractical and burdensome for the majority of patients. Beyond the inconvenience of monthly doctor's visits and monthly injections, the data argues that patients may be able to achieve similar visual outcomes with an as needed or treat and extend dosing regimen and they are likely receiving unnecessary injections. These unnecessary visits and injection translate to increased cost and waste to our healthcare system.

Additionally, each injection while potentially beneficial to improving visual outcomes carries risks. While the rate of infection is low, injections put the patient at risk for potential endophthalmitis. The reported incidence of endophthalmitis per patient receiving anti-VEGF therapy in multicenter clinical trials ranges from 0.019-1.6%.[5,6,17] This is a risk of about 1/100 per patient. There is evidence to also suggest that repeated injection may be associated with geographic atrophy, such that unnecessary injections should be avoided. A further analysis of the patients in the Comparison of Age-related Macular Degeneration Treatments Trial (CATT) showed that while there are many factors associated with geographic atrophy, ranibizumab use may accelerate geographic atrophy growth.[18] In addition to the increased burden to the patient and cost in the healthcare system, unnecessary injections also carry potential risk.

In the studies reviewed in this paper, the as needed treatment studies do show favourable outcomes, such as in the PrONTO and SUSTAIN trials. However, as needed treatment still relies on close follow-up and does not eliminate the burden of monthly follow-up visits. This dosing regimen does, however, eliminate some unnecessary injections and lower overall cost. A potential downside with this regimen is when patients are only treated for recurrent exudation, multiple recurrences overtime may disrupt retinal architecture and potentially compromise long- term visual outcomes.[6]

The treat and extend protocol seems to offer the most favourable alternative to the monthly regimen with a goal being to extend the interval between visits in order to maintain an exudation-free macula with the fewest number of visits and injections. This method sins to both reduce burden of visits, injections, and overall cost. While there have not yet been any large prospective trials comparing treat and extend to other dosing regimens, the LUCAS trail has shown promising results in its first year.

Apart from the above evidence based results, physicians must also take into account an individual patient's situation and preferences. Social factors such as the ability of a patient to travel to frequent visits, caretaker availability, level of independence of the patient, and availability of transportation are factors that cannot be ignored when deciding an appropriate dosing regimen. Additionally, the overall health of the patient is an important consideration. For example, a patient with multiple comorbidities who is often in and out of the hospital may be better suited for less frequent visits and injections than an otherwise healthy patient. Additionally, physicians may take into account the status of the other eye. For example, a provider might be more conservative and choose a maintenance strategy with regular injections in a patient who is monocular or has a large disciform scar in the other eye. Lastly, the physician must take into account patient preference when recommending and creating a follow-up and injection schedule.

CONCLUSION

There is no definitive evidence that one treatment regimen is superior to others in the trials presented in this review. However, the available evidence suggests that individualised treatment protocols provide a reasonable alternative to the monthly injection protocol first described in the landmark MARINA and ANCHOR trials. Among these, the treat and extend protocol seems to be the most favoured among clinical practice today. There is however a lack of data comparing prn and treat and extend methods head to head in a prospective trial. The treat and extend treatment regimen data also shows that the mean number of injections is likely to decrease with longer follow-up when patients are in the maintenance phase of therapy. This trend is evident in patients requiring fewer injections and less frequent follow-up in the second year of studies. There still remain several unanswered questions regarding exudative AMD treatment regimens, including the interval by which treat and extend protocols should be extended at each visit, how long these injections should be continued for, and whether this treatment interval changes for other drugs such as aflibercept (Eylea).

The current recommended dosing for aflibercept is once

every four weeks for the first three injections followed by once every eight weeks. The VIEW 1 and VIEW 2 studies, both phase II studies of nearly identical design, showed aflibercept dosed every two months after three initial monthly doses to be non-inferior to ranibizumab given every month. In year 2, patients received prn treatment, with a minimum of one injection every 12 weeks or quarterly. Over 96 weeks, patients receiving aflibercept had a similar visual acuity to those receiving ranibizumab but with an average of five fewer injections.[19] Eylea may be able to help in reducing the burden of injections and hospital visits without compromising visual outcomes, however it is costly and reimbursement for Eylea is currently only approved for patients who have failed treatment with Lucentis.

We additionally lack evidence based guidelines on what to do when patients become less responsive to an anti-VEGF medication. Non-responders are eyes that demonstrate persistent macular fluid or blood, leakage on fluorescein angiography, and vision loss despite repeated pharmacologic treatment. The terms tachyphylaxis and tolerance have been used to describe this decreasing therapeutic response to a pharmacologic agent with tachyphylaxis designating a more rapid onset of this lack of response.[20] Therapeutic approach may be tailored in these patients to alternate between bevacizumab and ranibizumab or change pharmacotherapy, however there are no set guidelines to approaching these patients.

Anti-VEGF medications have revolutionised the treatment of exudative AMD over the past two decades and patients with a potentially blinding disease have been able to regain vision. While there is still no clear cut best treatment regimen, evidence suggests individualised treatments may be safer and more efficient. As innovation creates new agents for the treatment of AMD, it is essential to choose the most effective and economical regimen for patients in order to decrease the overall burden on the patient, physician, and healthcare system.

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