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Review article

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A Comparison of Management Strategies and Treatment Results for Neovascular Age-Related Macular Degeneration with a Focus on the Treat-Extend-Stop Protocol

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Abstract

Neovascular Age-Related Macular Degeneration (nAMD) is a leading cause of blindness, but the management has been revolutionized by anti-vascular endothelial growth factor (anti-VEGF) agents. Three main treatment strategies have been developed to manage nAMD. The first method is fixed interval dosing, a mainstay of randomized clinical trials (RCT), where patients receive treatments on a monthly or bimonthly interval based on the anti-VEGF agent. Shortly thereafter, the pro-re-nata (PRN) method was introduced, where patients were treated as needed based on OCT status, usually preceded by three loading doses. Another method developed was the Treat-And-Extend regimen (TAE). Patients are treated until a dry macula is obtained and then the time interval between injections is gradually increased, usually by one to two-week intervals. A variation of the TAE protocol, termed Treat-Extend-Stop (TES), extends patients to a maximum interval of 12 weeks and then stops treatments after two injections, 12 weeks apart, if a "dry macula" is maintained. These patients are then monitored in a stepwise fashion, evaluating them four weeks after treatment is stopped and then increasingly at two-week intervals until the patients are monitored quarterly. Re-initiation of the TES protocol is begun immediately if a recurrence of the choroidal neovascularization (CNV) occurs. Using this method, patients' vision improved from 20/70 to 20/50 ($p<0.001$), or approximately 7.5 ETDRS letters at treatment cessation, with an average of 22 injections over three years of active treatment. True disease recurrence using the TES method in eyes that ceased therapy was observed in 29.4% of eyes, with an average of 14 months to time of recurrence. Average vision initially decreased to 20/60 during recurrence, however recovered to 20/50 after restarting TES injection protocol. Thus, the TES strategy may provide visual improvement and stability, leading to disease remission and cessation of anti-VEGF therapy without loss of vision.

Keywords: Treat-and-Extend; Treat-Extend-Stop; neovascular Age-Related Macular Degeneration (nAMD); Anti-VEGF; Recurrence

Introduction

Age-related macular degeneration (AMD) is the third leading cause of blindness in the world [1]. The disease may convert from the degenerative form, "dry macular degeneration", to the neovascularization form, "wet macular degeneration", at a rate ranging from 10%-15% [2]. Currently, relatively little scientific evidence exists regarding methods to prevent this conversion, making AMD the leading cause of unpreventable blindness globally [1].

Anti-VEGF agents gained widespread adoption, beginning in September 2005 following the positive results of bevacizumab (Avastin, Genentech, San Francisco, CA) used in an off-label fashion [3,4]. The truncated murine antibody counterpart, ranibizumab (Lucentis, Genentech, San Francisco, CA) became available in 2006 [5] and the soluble VEGF decoy receptor aflibercept (Eylea, Regeneron, Tarrytown, NY) became available in November 2011 [6]. While all three agents have demonstrated efficacy in randomized control trials (RCT) and in retrospective studies, differences in visual improvement or stability may, arguably, be attributed more to the treatment timing and methodology as opposed to the anti-VEGF agent used. Three anti-VEGF treatment protocols are typically used in the management of nAMD. The first is fixed interval dosing, with injections typically performed monthly or every other month. Many of the RCTs favor this approach [4-12]. This has also been studied clinically in a retrospective fashion, with good visual outcomes, even in the long term [13,14]. A pro-re-nata (PRN) method was then developed to limit treatment burden of monthly anti-VEGF therapy for both the patient and physician. The method typically begins with three monthly loading injections, and if the disease process stabilizes, then the injections are held. Injections are then reinitiated upon observation of increased of fluid or exudation on OCT. A number of RCTs have assessed this treatment strategy, including several of the treatment arms of the HARBOR and CATT trials [9,12] Many extension trials of RCTs, such as the CATT extension and SEVEN-UP trials, as well as short and long-term retrospective studies have also been performed, with longer studies typically demonstrating poorer visual outcomes [15-24].The final protocol to be discussed is treat-and-extend (TAE) method and is the predominant treatment strategy used amongst retina physicians in the United States. It has potential to decrease treatment burden, like PRN dosing, while maintaining the visual gains of fixed dosing. Under this treatment methodology, patients are typically initiated with three loading doses given one month apart [25-29]. Following the loading phase, treatment intervals are extended by one to two weeks at a time if a "dry" macula is maintained on SD-OCT, typically beginning from four weeks, until a typical maximum of 10-12 weeks is reached. Subjects are then continued on a 10 to 12-week schedule; however, it is possible that some patients never reach the maximum extension interval. Some patients require continuous treatment at shorter time

intervals due to persistent fluid, while others experience a decrease in vision or increase in exudation and require shortening of the treatment time interval in order to obtain adequate control of the disease process. For those patients that are extended to the 10 to 12-week maximum, a variation of the TAE method termed Treat-Extend-Stop (TES) has been developed by Adrean et al. [28,29]. Under the TES method, patients who reach the 12-week extension interval receive two injections 12-weeks apart. Patients are then brought back 12 weeks later, and if a "dry" macula is still present, then treatments are held, and patients are then carefully monitored for signs of recurrence. These patients' choroidal neovascularization (CNV) is considered to be in remission. Patients are brought back four weeks later and are assessed in a stepwise fashion, increasing the time interval between visits by two weeks until 12 weeks are reached. The patients are then monitored quarterly. Patients are instructed to return immediately if they notice decreased vision or an increase in metamorphopsia. If this occurs, treatment is reinitiated immediately, and the TES protocol is started again from the beginning.

Discussion

Effect of distinct treatment methods on visual outcomes

Treatment with the three agents, bevacizumab, ranibizumab or aflibercept, has demonstrated comparable efficacy in RCTs and retrospective studies. In the MARINA, ANCHOR, HARBOR and CATT trials, monthly ranibizumab injections on average improved vision from 6.5 to 11.3 ETDRS letters [4,5,9-12]. The CATT trial also demonstrated similar vision between bevacizumab and ranibizumab, with the bevacizumab arms gaining 5.0 to 7.8 letters at two years [12]. The VIEW 1 and 2 studies evaluating intravitreal aflibercept had visual gains of 8.4 letter gain at 52 weeks, which demonstrated that it was non-inferior to ranibizumab [30]. Various retrospective studies likewise reported visual improvements of 5.0 to 9.0 letters [25,30].

Differences in visual outcomes became apparent, however, once the injection frequency or interval was changed. Quarterly injections in the PIER trial resulted in decreased vision at one and two years (-0.2 and -2.3 letters for 0.5 mg ranibizumab *vs.* vision at onset of therapy) compared to other monthly dosed RCTs (+6.5 to +11.3 letters *vs.* baseline) [4-12]. Those patients who were later rolled-over to monthly injections in the PIER study subsequently recovered some vision, from 2.9 to 4.3 letters, but these patient's visual acuity (VA) never caught up to the monthly cohort [7,8].

The PRN methodology may also produce inferior vision compared to fixed interval dosing. However, it is still better than the natural history and photodynamic therapy [30-32]. While both the HARBOR and CATT trials reported visual gains using the PRN protocol, there was a trend to decreased VA at the end of year one, and VA was significantly worse ($p<0.05$) when compared to monthly dosing, in both studies after two years [9-12]. In the SEVEN-UP and CATT extension studies of those landmark RCTs, subjects were largely transitioned from a fixed interval to a PRN strategy [15,16]. The SEVEN-UP study reported a mean change of -19.8 letters from peak visual acuity (VA) at the end of the ANCHOR or MARINA trials, and an 8.6 letter decrease from the initial presenting vision [16]. Likewise, the CATT extension study averaged a loss of 11 letters from the year two results or -3.3 letters from baseline vision at trial initiation, after transitioning to the PRN method beyond the two-year timepoint [15]. These results have also been seen in multiple retrospective studies [20-24].

The TAE strategy and its variant, the TES protocol, have proven promising by achieving visual outcomes comparable to fixed doxing and superior to PRN methods. A study by Wycoff et al. demonstrated that TAE methodology was non-inferior to fixed monthly dosing using ranibizumab (+10.5 and +8.7, respectively, $p=0.64$) [33]. Interestingly, in studies by Hatz et al. and Cohen et al., visual function improved after switching from a PRN to TAE method, despite more frequent office visits in the PRN group [19,34]. For example, BCVA initially increased in the loading phase (0.39 to 0.55 logmar), but then decreased after transitioning to a PRN strategy during the maintenance phase (0.49 logmar) [19]. Following TAE transition, BCVA improved to 0.55 logmar, and was maintained throughout 12 months (0.56 logmar) [19]. On average, there were 1.05 visits per month using the PRN strategy versus 0.73 per month using TAE [19]. These effects have been especially notable when following patients over the long-term, anywhere from three years to eight years [28,29,35]. The longest TAE/TES studies to date, and possibly for any treatment methodology, are those conducted by Adrean et al [28,29]. In the first study, patients were treated for approximately 33 months until reaching cessation of therapy (disease remission) and were subsequently carefully monitored [28]. Eyes at the end of 33 months had an average improvement from 20/70 to 20/50 (approximately +7.5 ETDRS letters), with 60% of eyes achieving greater than 20/40 vision. In a subsequent study, Adrean et al. evaluated the impact of long-term TES injections for eyes not necessarily achieving cessation of therapy [29]. Patients had visual gains of 9.7 letters, at an average of 6.5 years of treatment (50 injections), which was maintained with an improvement of 8.7 letters, at an average treatment time of 8.0 years. Patients were treated at an average of 5.4 weeks at 6.5 years, and 6.4 weeks at final follow-up of eight years. Notably, these visual outcomes are comparable to two-year results of landmark clinical trials using monthly fixed dosing regimens (+6.5 to +11.3 letter improvement) and substantially better than long-term studies utilizing the PRN strategy (+1.4 to -10.3 letters change *vs.* baseline) [4,5,9-12,22,24,36].

Treatment methodology on disease recurrence

A number of risk factors, including older age, male gender, subtype of AMD and VA at baseline, among others, may contribute to increased breakthrough exudative disease or need for retreatment [37]. The time for vessel proliferative cycling may also explain why proactive treatment using monthly or TAE/TES strategies may produce better visual outcomes and less breakthrough exudation compared to the PRN method [38]. It is suggested that the development of CNV follows a 45 to 60-day cycle after intravitreal injection, with vessel pruning occurring within 24 hours of injection and reaching a maximum between 6-12 days [38]. Sprouting and opening of new vessels typically occurs within 20-50 days later [38]. After subsequent treatments, the time between sprouting and opening of neovascular vessels appear after a longer period of time [38]. Because the PRN treatment strategy is reactive, the time between onset of breakthrough disease to detection and treatment of increased exudation may be untimely [19,34]. Undertreatment or delayed treatment using the PRN protocol thus may more often fall within, or even beyond, the typical time frame for new vessel development; whereas, monthly or TAE/TES regiments may continue to suppress disease. The lengthening of the CNV cycles allows for extended treatment intervals. Thus, new or increased exudation may not represent a true disease recurrence, but rather is a symptom of undertreated disease. Over time, with multiple episodes of "mini recurrences", the visual acuity is ultimately impacted, and patients overall lose vision [19,34].

Various studies have reported "recurrence" rates of disease during anti-VEGF treatment, however the definition of disease recurrence remains ambiguous. Some studies consider disease recurrence to be any new evidence of fluid after a dry macula is achieved regardless of time [39]. However, a better definition of recurrence is described by studies reporting a new onset of neovascularization after achieving defined criteria for disease remission (cessation of therapy), for example, 4 months minimum of a "dry" macula without treatment [28]. Otherwise, new onset of fluid may merely be symptomatic of active breakthrough disease during treatment. Studies evaluating the anatomical location of neovascularization will help further elucidate true disease recurrence.

Currently, very few studies report CNV recurrence following disease remission. To our knowledge, only two retrospective studies have investigated this phenomenon. Haddad and colleagues evaluated 132 eyes over an average final follow-up period of 7.75 years [21]. After a fixed loading schedule, eyes were transitioned to PRN dosing. Although 63% (83/132) eyes entered into remission (12 months of no therapy) at least once (51%) of eyes experienced recurrence of CNV. Moreover, initial visual improvement was not maintained and returned to below baseline prior to treatment (+5.0 letters at 12 months post-treatment *vs.* -3.41 letters at 7.75 years; Δ=-8.41 letters). In contrast, Adrean et al. reported that 37.3% (143/385) of eyes managed using a TES method were able to achieve cessation of therapy (four months without treatment) after an average of 33 months of extension treatment and 27 months of average follow-up [28]. Of those eyes, 29.4% experienced a recurrence of neovascularization, at an average time to recurrence of 14 months. Average vision improved from 20/70 to 20/50 at treatment cessation (approx. +7.5 ETDRS letters), decreased to 20/60 during recurrence, and recovered to 20/50 following re-initiation of TES protocol [28]. Thus, the TES method appears to be superior compared to the PRN strategy over the long-term, to limit disease recurrence and maintain visual improvement.

Conclusion

The management of nAMD for most patients, regardless of the choice of anti-VEGF agent, may be best achieved using a TAE/TES regimen. This proactive and individualized treatment strategy is superior to monthly fixed dosing as it appears to achieve equivalent visual outcomes with decreased treatment burden and possibly fewer adverse outcomes. Moreover, the TAE/TES protocol has numerous benefits over a PRN schedule, including greater visual improvement, achievement of disease remission, and decreased recurrence of neovascularization, among others, particularly in the long term. Future studies elucidating the mechanism of disease recurrence will help further optimize anti-VEGF therapy in the management of nAMD.

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