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Review Article

Evaluation of nAMD Treatments Efficacy on Patient's Full Adhesion to the Follow-Up Treatment

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Abstract

Purpose: Ophthalmologists increasingly depend on intravitreal injection drugs to advance their treatment options for neovascular nAMD. These options require multiple visits of the patient to the center, along with continuous follow-up that can go for years without any hope of definitive healing or any end-treatment date. This constitutes a mental and psychological transportation and cost burden on nAMD patients who naturally become prone to withdraw the treatment. Cost-effectiveness schemes analyses need to be appropriate and of good quality to support correct decisions to adopt a treatment scheme. In this study, we report the quality, validity and usefulness along with the burden of each available scheme for therapies for nAMD, in order to determine the best regimen treatment that prevents the patient to fall in desperation and withdraw the treatment.

Methods: A systematic review was performed to include Pro-re-nata (PRN), Treat-and-Extend (TREX) and Treat-and-Observe (TROB) regimen. Quality and validity regarding the cost-effectiveness and time burden were assessed based on current general quality follow-up criteria and on elements that are specific to the field of ophthalmology.

Results: All three regimen consist first of 3 monthly injections. After that the interval between the different regimens vary from monthly follow-up (PRN regimen), to extended fixed intervals (TREX regimen) or extended intervals until the reoccurrence of the symptoms (TROB regimen). Cost-effectiveness results vary slightly between the three regimens, but the patients seem to adhere more to the TREX regimen.

Conclusion: TREX strategy to deal with neovascular AMD seems to offer the opportunity to individualize management while maintaining the advantage of better conserving the comfort of the patients (injection number, number of visits) and reducing the burden of care and the cost of care delivery.

Although TREX approach has barely reached the best visual outcomes provided by monthly injections or PRN, it may seem a more accurate choice for patients that have trouble to come in for monthly visit, especially that certain patients may require 10 years or longer duration treatment.

Keywords: *Age-Related Macular Degeneration (AMD); Ranibizumab; Aflibercept*

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries and is responsible for 8.7% of all blindness worldwide [1-3]. AMD prevalence is expected to increase with population ageing projections. Treatment options for AMD patients are still limited and vision does not clearly improve for most people especially patients with wet AMD [4]. Available current

treatments include several anti-vascular endothelial growth factor (VEGF) medications that are injected directly into the vitreous cavity: Ranibizumab (Lucentis), bevacizumab (Avastin), and more recently Aflibercept (Eylea). The aim of Anti-VEGF drugs is to reduce the level of VEGF that stimulates abnormal blood vessel growth and vessel permeability in the retina, thus helping to slow or sustain vision loss in wet AMD. Those medications include many side effects such as blurred vision, eye irritation, eye pain and photosensitivity. The injections are given at different intervals: first, three times monthly injections, then it continues either with monthly intervals, or other fixed intervals, or successively extended intervals. Retinal stability is determined by Ocular Coherence Tomography (OCT), which allows the doctor to identify fluid in the central retina that determines the intervals for intravitreal injections. There is no doubt the permanent uncorrectable loss of central vision due to AMD has significant psychological implications for nursing care and for the mental stability of the patients. Side effects together with the multiple injections necessity and monitoring require a scheduling for unhopeful patients and caregivers, thus becoming a full-time worry for the patient. This results in a significant burden on patients and their family and nurture desperation, enhancing the risk of withdrawing the treatment.

The different therapeutic follow-up schemes may represent - alone or together with visual outcomes and mental state - important factors that may influence differently the willingness of the AMD patients to fully adhere to or withdraw the treatment. Although it is true that therapy will not recover significantly lost vision, much can be done to help improving the remaining vision and maintain the willingness of the patient to continue the treatment.

The aim of this study was to assess the impact of the different schedule treatment schemes currently adopted, on the adherence rate of nAMD patients to the treatment, in order to identify the best available follow-up scheme for treatment that gives these patients a more positive outlook, encourages them not give up on the treatment.

Follow up intervals

Ranibizumab and aflibercept are usually initiated with a 'loading' phase of three injections given monthly for three consecutive doses, followed by a maintenance phase in which patients are monitored with BCVA, history, examination, OCT and/or angiographic examination. In principle the interval between two doses should not be shorter than 4 weeks normally for ranibizumab or 8 weeks for aflibercept, unless hyperactive lesions occur. Only now, the follow-up strategies adopted became numerous, yet very important for the utmost effectiveness of the treatment. Evidence suggests aflibercept treatment outcomes are similar to those of ranibizumab [5]. However, MARINA and ANCHOR study stated that Aflibercept was superior to Ranibizumab in significantly improving visual and anatomic outcomes in the younger patients, unlike older patients (≥ 85 years old) who experienced no change in BCVA.

Pegaptanib (Macugen) is practically unused anymore after the current recommendations from NICE that it is not cost-effective as a first line therapy in the treatment of wet AMD. Otherwise it was given by 6 weekly injections. After that, disease activity is denoted by retinal, subretinal, or sub-RPE fluid or haemorrhage, as determined clinically and/or on OCT, lesion growth on FFA (morphological), and/or deterioration of vision (functional).

At the light of the disease activity, the corresponding ophthalmologist decides whether to continue the treatment or interrupt it temporarily or permanently: usually the treatment is continued when there is persistent evidence of lesion activity, when the lesion continues to respond to repeated treatment and when there are no contra-indications or serious adverse effects yet denoted. The treatment is ceased in the rare cases where the injection causes certain type of allergies or other serious damages, otherwise the treatment is temporarily interrupted when disease activity has disappeared or when one or more adverse events related to the drug or the injection procedure have manifested.

Understanding patient withdrawal

Despite the increase in vision with the introduction of anti-VEGF agents, compared to previously popular "destructive treatments," such as laser photocoagulation and photodynamic treatment, anti-VEGF agents therapy still require repetitive and costly intravitreal in-

jections that also carry the inherit serious adverse events risk of infection, endophthalmitis, cataract, vitreous haemorrhage, retinal tears, and detachment. IVT Procedure Guidelines are available on the RCOphth website. http://www.rcophth.ac.uk/page.asp?section=451&sectionTitle=Clinical+Guidelines_intravitreal_injections_guidelines2009.pdf.

Naturally Patients with subretinal hemorrhages secondary to AMD are psychologically distressed as a result of acute loss of vision. Mozaffarieh., *et al.* found that patients were significantly more distressed at their 2-week follow-up in comparison to controls ($P < 0.01$), but no significant difference in psychological scores at the 4-month follow-up ($p > 0.32$) [6].

As calculated by the Royal College of Ophthalmologists in 2013, licensed anti-VEGF treatment only improves vision in a third of patients; the majority maintain vision and some 10% do not respond to therapy. Few cases though, develop hypersensitivity reaction or even reduction in BCVA in the treated eye with deterioration of the lesion morphology despite optimum treatment, thus regressing instead of progressing, and this challenging reality certainly irritates the patient towards any further will of pursuing the treatment.

Some of the patients are over 90 years-old and just getting them into the clinic can be a difficult ordeal for themselves and their family members. Moreover, when patients are advised of the need for frequent monitoring after starting a course of intravitreal drug treatment for AMD and when they know they'll have to visit the clinic every 4-8 weeks-depending on the licensed anti-VEGF used - for up to and beyond 2 years Only then, they naturally start feeling the burden of this long repetitive and little effective treatment.

Efficacy of follow-up regimen son visual function in patients with AMD

Although many patients with AMD benefit from the treatment and adhere with IVTs, a significant proportion of patients on the other hand, either refuse to initiate the therapy or eventually abandon midway

Pro re nata (PRN) regimen

A pro re nata (PRN) regimen is a scheme consisting of 3 monthly injections followed by subsequent reevaluations at 4 weeks intervals for Ranibizumab and 8 weeks for Aflibercept. Subhi., *et al*. demonstrated a significantly improved BCVA at 4 months with Aflibercept in patients ≥ 90 following the PRN treatment regime [5] (Table 1). In fact, 8 weeks interval gives more flexibility from a clinical point of view. Some patients needed additional injections within the 4 weeks for Ranibizumab and within the 8 weeks for Aflibercept. Patients treated with Ranibizumab needed slightly more injection numbers than those treated with Aflibercept. Moreover, Rasmussen A., *et al*. in 2013 [7], found that in 600 eyes of 555 patients treated with Ranibizumab for AMD for 4 years, one third of the eyes were still receiving active treatment after 4 years and had stable visual acuity. One third of fellow eyes (eyes at risk) started treatment during the 4 years. One fifth of discontinued eyes resumed treatment, indicating that close follow-up should be maintained for patients discontinued because of disease inactivity (Table 1). The ocular complication rate was 0.2%, and the mortality rate was below expected.

BCVA improvement/ Injection number	PRN	TREX	TROB	Number of eyes	Number of Withdrawal (eyes)
Calvo P., *et al*. [11] (at 3 years follow-up)	-	BCVA improved in 42.4% of the eyes/20.31± 6.6 injections	BCVA improved in 24.1% of the eyes/18.4± 7.1 injections	30 eyes in TREX group, 30 eyes in TROB group	-
Oubraham., *et al*. [15] (at 12 months follow-up)	-	BCVA gain +10.8 ± 8.8 letters/ 7.8 ± 1.3 injections	BCVA gain +2.3 ± 17.4 letters/5.2 ± 1.9 injections	52 eyes in the PRN group and 38 eyes in the TREX group	-
Wykoff., *et al*. [13] (at 1-year follow-up)	BCVA improved by 9.2/ 13 injections	BCVA improved by 10.5 letters / 10.1 injections	-	60	3/60
Vardarinos A., *et al*. [14] (in 2 years follow-up)	-	BCVA gain of 8.3 letters (mean 68.8 ± 11) at 1-year follow-up and 5.2 letters (mean 65.7 ± 12.3) at 2 years follow-up/ 12.1 ± 2.8 injections over the 24-month period		56	10/56
Subhi., *et al*. [5] (in 2 years follow-up)	BCVA improved at 4 months (mean change 3.2 (SD: 15.5) ETDRS letters, P=0.036); BCVA stabilized at 12 and 24 months (mean change 1.5 (SD: 16.5) ETDRS letters, P=0.342; mean change −2.2 (SD: 20.1) ETDRS letters, P=0.288)/ 5.7 injections for 2 years.	-	-	116	59/116
Rasmussen A., *et al*. [7] (at 4 years follow-up)	Unchanged BCVA (0.32; P>0.3)/5.5 injections per year. In the 67 eyes that resumed treatment, final BCVA decreased from from 0.38 to 0.15 (P = 0.001)	-	-	192 67	278/408
Garcia., *et al*. [8] (in 1year follow-up)	BCVA was higher at 1-month follow-up than at 1 year (logMAR −0,29±0,44 vs logMAR 0,42±0,73; *p*=0,016)/~ 10 injections	-	-	21	-
Westborg., *et al*. [10] (at 1-year follow-up; and at 7 years follow-up)	BCVA increased from 57.8 ± 17.7 ETDRS letters to to 62.8 ± 16.4 ETDRS letters at 1 year then mean change of -1 letters at 7-year follow-up/The mean number of injections during the first treatment year increased from 4.3 ± 1.9 in 2008 to 5.9 ± 2.9	-	-	322	-

Table 1: *Comparison of BCVA changes and anti-VEGF injection numbers between PRN, TREX and TROB regimen in different studies.*

Additive results by Garcia., *et al.* 2016 [8], showed also that monthly follow-up, between the IVT series in patients undergoing surgery for sub-macular hemorrhage associated with AMD, is highly recommended to preserve postoperative VA.

However, contrary to common interpretation, no change, or a limited decline, in the outcome (visual acuity) can still imply that the patients are better off with the treatment than with no treatment [9,10], recently reported that the duration of symptoms before treatment decreased, while VA at baseline and after 1 year of treatment increased over the years and so did the number of injections. Hence stopping the treatment may not be appropriate since it was effective in at least a proportion of patients. Nonetheless, this being said, it is clear that such noticeable improvements come with a regular frequent follow-up which may constitute a burden for the patients thus reduce their long-term motivation.

Now, regarding the adherence to treatment and efficacy in treatments in the above 90 years old AMD patients, the authors reported a significant correlation between the severity of the disease and the time of abandonment, as they found that patients feeling burdened by the treatment and those suffering from fibrotic or untreatable lesions opted out within the first year, whilst the patients with inactive CNV or dry macula withdrew the treatment only after the first year [5]. During the two-year follow-up, 59/116 patients (51%) in total discontinued the treatment, although all the patients benefited from free-of-charge transportation to the hospital. Also, despite these impressive results of PRN treatment with ranibizumab in Calvo P., *et al.* study [11] the burden on patients, their families and clinicians to sustain monthly visits showed to cause a great deal of physical and emotional stress in addition to the economic burden of resources used. Additional concern lies in that a significant number of patients refused to continue with injections and dropped out of the practice.

Treat-and-Extend (TREX) regimen

This burden of getting old patients into the clinic regularly has pushed 66.7% of US retinal physicist and a third of international retinal physicists to prefer more individualized treatment plan like Treat-and-Extend (TREX) as one solution. TREX is a dosing strategy that enables patients with wet AMD to go as long as 12 weeks between office visits and injections. The retina is first cleared from macular fluid and retinal hemorrhages with a series of 3 monthly Injections until the patient achieve the maximum response. Than the interval between treatments is extended, 2 weeks at a time, until a maximum of 12 weeks as long as vision gains are maintained, and the retina remains dry and stable, based on OCT. Otherwise, the patient is given another set of 3-monthly injections and continued monthly injections until disease state was deemed inactive, then re-treatment interval is gradually increased 2 weeks each time.

An algorithm has been designed that recommends a maximum interval of 12 weeks between injections, and if minor changes occur between visits (such as a small increase in fluid) then all to do is go back to the interval that kept them dry. Only in the situation of a major event like large hemorrhage, would the patient be reverted to monthly treatment. Thus, TREX regimens have the advantage of coping with the unknown in a personalized manner because of the great range of variability between patients prohibiting the prediction of how each patient will respond or not to the treatment. More than a dozen small or retrospective published studies reported positive effects of TREX outcomes in eyes with nAMD, beside LUCAS trial that met level 1 criteria of demonstrating efficacy [12]. Recently, authors reported 7 (18%) among TREX patients were maximally extended, 4 (10%) demonstrated fluid at every visit, and at month 12, 18 (45%) had achieved an extension interval of 8 weeks or more; the mean maximum extension interval between injections after the first 3 monthly doses was 8.4 weeks [13].

Also, in one more paper, Wykoff., *et al.* revealed 57/77 eyes (95% of the eyes) completed the 12 month follow-up, at which point mean BCVA improved by 9.2 and 10.5 letters in the monthly and TREX cohorts, respectively, consistent with the registration trials ANCHOR, VIEW1 and VIEW2, as well as with The TREX outcomes reported by Abedi., *et al.* from a single-arm, prospective analysis involving patients treated with both bevacizumab and ranibizumab, through 2 years compared with monthly dosing in ANCHOR and MARINA [13]. Three patients withdrew consent at weeks 15, 19, and 27 in TREX group because of temporal arteritis, diagnosis of lung cancer, and meningitis, respectively. The mean number of injections administered through month 12 was 13.0 in the monthly cohort and 10.1 in the TREX co-

horts (P < 0.0001) (Table 1), thus effectively yielding 3 fewer treatments within 12 months, hence, 3 fewer office visits and travel burden. Favorably, such clinical effectiveness of TREX regimen achieving favorable outcomes with a significant reduction of the treatment burden compared to monthly PRN was also noticed in a first UK real-life study of a TREX treatment protocol with ranibizumab for nAMD in a 24-month period [14] (Table 1). This study demonstrated a mean BCVA of 8.3 letters at month 12 and 5.2 letters at 24 months compared to baseline, along with anatomical improvements. Twenty-seven eyes of 56 achieved a treatment interval of 10 weeks or more a month 12, while the respective number at month 24 was 20 eyes (43.4% N = 46).

Moreover, considering that the pharmacokinetic properties of anti-VEGF drugs may play a larger role in patients aged ≥ 90 years, which are in risk of under-treatment, there may also be a potential for a larger gain using a TREX regime.

Nonetheless, the dilemma arises again when even within a TREX strategy, less frequent dosing can sometimes result in less optimal visual gains, as elegantly illustrated in the Fight Retinal Blindness observational registry involving 1011 neovascular AMD patients from Australia and New Zealand managed with a TREX approach [13].

In addition, most TREX patients who demonstrated recurrent exudative disease activity (17/24 [71%]) were unable to extend beyond their initial maximum extension interval [13]. Only 3 patients (13%) were able to maintain a dry macula at an interval of 2 weeks or more beyond their initial maximal extension interval on challenging this interval. Moreover, although visual and anatomic gains were comparable with those obtained with monthly dosing, more ocular and serious adverse events were noted with the TREX method comparing to monthly dosing (25% and 15% of the TREX cases vs 13% and 0% of the monthly-treated cases).

Treat-and-Observe (TROB) regimen

Another study compared the 3-year outcomes of the TREX regimen versus the PRN or Treat-and-Observe (TROB) regimen for wAMD patients > 65 years-old, treated exclusively with ranibizumab. TROB regimen consists of 3 monthly injections, followed by an as-needed decision to treat, based on monthly check-up of the worsening of BCVA, disease activity on fundoscopy and OCT evidence of retinal thickening with intra-retinal fluid (IRF) or subretinal fluid (SRF) [11]. Results at 36 months showed VA improved in 42.4% and 24.1%, while 33.4% and 62.1% remained stable for TREX and TROB groups, respectively, with neither final VA differences nor final injections number received (20.31 ± 6.6 in TREX vs 18.4 ± 7.1 in TROB) differences. Only at 6 and 12 months, the total number of injections was slightly higher in TREX than TROB [11]. Probably more important to the patient is the fact that 42.4% of patients in the TREX group and 24.1% in the TROB group had VA improvement from baseline. In contrast, Oubraham., *et al.* [15] reported greater VA improvement in the TREX group (N = 38) than the TROB group (N = 52) in 1 year (+10.8 ± 8.8 versus +2.3 ± 17.4 letters, p = 0.036), and the improvement in BCVA in the TREX group after 3-year follow-up was almost double than the TROB group (42.4% vs. 24.1%, p = 0.08) in Calvo P., *et al.* study.

The 2012 American Society of Retinal Specialists Preferences and Trends survey revealed the majority of Retinal Specialists members have turned to non-monthly regimens, with 66.7% using TREX and 23.7% TROB.

In the light of all these challenges, the retina specialists of our ophthalmic Center Monticelli-Paradis of Marseille elaborated the know-and-treat strategy which consists mainly of following directly a TREX strategy after the first 3 monthly loading phase, unless recidivism is occurring. In this latter case, an intermediate phase of PRN is adapted before switching to TREX. By the end of 3 to 4 years of follow-up, the patient usually exits the treatment with either TREX or PRN strategy.

Efficacy of follow-up services on patient's motivation to continue the treatment

The permanent loss of central vision associated with AMD has significant psychological implications for nursing care and for the patient's energy to continue the treatment.

In a recent large clinical trial conducted on AMD patients who had more than 5 anti-VEGF injections from a minimum of 3 months with no impending further anti-VEGF treatment, Deemer., *et al*. [16] distinguished the patients who benefited from behavioral activation

(BA) from those who benefited from supportive therapy (ST) to assess the effectiveness of proper paraclinical support on the treatment outcomes regarding BCVA and patient depression rate. BA is a structured behavioral treatment that aims to increase adaptive behaviors and achieve valued goals. ST is a nondirective, psychological treatment that provides emotional support and controls for attention.

Deemer., *et al.* found that BA plus low vision rehabilitation (LVR) provided by an occupational therapist (OT-LVR) services in the patient's home following conventional low vision ST optometry services, are more effective than conventional optometric low vision services alone for those with mild visual impairment. Indeed, improvements in functional vision measures were seen in both the BA + OT-LVR and ST groups at the goal level (d = 0.71; d = 0.56 respectively), but at the task level, BA + OT-LVR patients showed more improvement in reading, inside-the-home tasks and outside-the-home tasks, when compared to ST patients. Those observations suggest that a more delicate follow-up like an integrated mental health and low vision intervention by an occupational therapist is crucial for AMD patients acquiring greater improvements of visual functions, maintaining their satisfaction about the treatment, halving the incidence of depressive disorders, hence raising their energy and hopes in pursuing the treatment. The same results were also observed in an older study of BW., *et al.* in 2014 who showed that 11 BA + LVR subjects (12.6%) and 18 ST + LVR subjects (23.4%) developed a depressive disorder at 4 months [17]. 11% of the ST + LVR group patients depressed and withdrew the treatment at 4-month follow-up, while 6.25% of the BA+LVR group patients depressed and withdrew the treatment at 4-month follow-up [17-19]. Thus, promoting to interactions between ophthalmology, optometry, rehabilitation, psychiatry, and behavioral psychology effectively prevent depression in AMD population and encourage adherence to the treatment.

Conclusion

TREX strategy to deal with neovascular AMD seems to offer the opportunity to individualize management while maintaining the advantage of better conserving the comfort of the patients (injection number, number of visits) and reducing the burden of care and the cost of care delivery.

Although TREX approach has barely reached the best visual outcomes provided by monthly injections or PRN, it may seem a more accurate choice for patients that have trouble to come in for monthly visit, especially that certain patients may require 10 years or longer duration treatment.

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