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Editorial

"Triple and Plan" (TriPla) regimen for long lasting new generation intravitreal anti-VEGF

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Abstract

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) medications are the primary treatment for neovascular age-related macular degeneration (nAMD). However, frequent administrations pose significant burdens on patients, healthcare providers, and systems. The treat-and-extend (T&E) regimen, which adjusts treatment intervals based on patient response, aims to reduce injection frequency while maintaining disease control. The "Triple and Plan" (TriPla) regimen, developed during the COVID-19 pandemic, further optimizes treatment by scheduling three consecutive injections, thus minimizing clinic visits while ensuring adequate treatment.

Newer agents such as Faricimab, Aflibercept 8 mg, and Brolucizumab offer longer-lasting effects, potentially extending treatment intervals. Faricimab, targeting both Ang-2 and VEGF-A, requires fewer injections and visits under the TriPla regimen compared to traditional T&E. Aflibercept 8 mg, with its higher concentration, promises extended intervals up to 16 weeks, reducing the injection frequency. Brolucizumab, notable for its small size and effective tissue penetration, also offers prolonged therapeutic effects but requires careful monitoring due to potential adverse events.

In the first two years of treatment, patients using the TriPla regimen with these new drugs would undergo a slightly higher number of injections but with fewer clinic visits compared to the T&E regimen. The TriPla approach optimizes scheduling and reduces the workload on specialists, potentially improving patient care and healthcare system efficiency. These advancements in treatment regimens and drug formulations present significant benefits in managing nAMD, balancing effective disease control with reduced healthcare burdens.

Keywords

Age-Related macular degeneration < RETINA, RETINA, techniques of retinal examination < RETINA, retina - medical therapies < RETINA, retinal pathology / research < RETINA

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Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) medications are currently the primary treatment for neovascular age-related macular degeneration (nAMD).[1] However, these treatments have a limited duration of effectiveness, necessitating frequent administrations and regular visits, which place a significant burden on doctors, patients, and the healthcare system.[2] The ultimate goal of nAMD treatment is to minimize disease activity,[3] so there is a need for newer agents with longer-lasting therapeutic effects to enhance patient care and visual outcomes.[4]

To extend the interval between injections, a treat-and-extend (T&E) regimen was proposed.[5,6] In this

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approach, the treatment interval was gradually increased by 2–4 weeks if no signs of recurrent exudation were observed. If recurrent exudation was detected during a follow-up visit, the treatment interval was shortened to the previous duration. The timing between visits was tailored based on the patient's response to the treatment. The goal of the T&E regimen is to maintain a macula free of exudation while reducing the number of intravitreal injections, office visits, and examinations.[7]

The "Triple and Plan" (TriPla) treatment regimen was proposed by Sacconi et al. during the COVID period to ensure an adequate number of intravitreal injections for patients and reduce the number of clinic visits. This regimen involves booking three successive intravitreal injections at the same time once the treatment is indicated. The interval between the last injection of the previous cycle and the first of the new cycle is the same as the interval between the first and second injections of the new cycle. After the second injection, a third injection can be administered one or two weeks later than the current treatment interval.

A follow-up visit is scheduled concurrently with this last injection. At this point, one of two scenarios can be followed: if the patient shows no signs of activity [i.e., absence of sub- and/or intra-retinal hyporeflective exudation or subretinal hyperreflective material (SHRM) using structural optical coherence tomography or hemorrhages at fundus examination], the new cycle is set by keeping the last interval as the reference interval and extending the interval between the second and third injections of the cycle by one or two weeks. If the patient shows signs of activity, a new cycle of three injections can be booked, reverting to the previous interval and extending the interval for the third injection by one or two weeks.[8]

Faricimab is the first humanized, bispecific IgG monoclonal antibody specifically designed for intraocular use through intravitreal injection. It independently targets and neutralizes both Ang-2 and VEGF-A, providing dual inhibition of two separate pathways implicated in the pathology of nAMD.[9]

For its use in AMD, a loading dose of four monthly injections is recommended, after which the treatment interval should not be less than eight weeks. A triple regimen for this drug would involve four injections at four-week intervals followed by two injections at eight-week intervals and a third injection at a 12-week interval. By the 40th week, alongside the seventh injection, based on the treatment response, a new triplet can be set with the first injection at a 12-week interval or reducing the interval to eight weeks, administering the first injection of the new cycle in the 48th week from the start of treatment. In any case, the patient would undergo eight injections and two visits (baseline and week 40^{th}) in the first year (Figure 1). In any case, aside from the two visits considered mandatory by this treatment regimen, the patient may be seen at other times according to the specific evaluations of the clinician or subjective variations in symptoms reported by the patient themselves. From week 52 to week 104 (second year of treatment), the triplet regimen allows, in the best possible scenario, for four injections and one follow-up visit (at week 80) or, in the worst case, five injections and two follow-up visits (at week 68 and week 96). In comparison, the T&E regimen, in the best case (managing to achieve q24 without ever needing to reduce the interval between injections), allows for two intravitreal injections and two follow-up visits, while in the worst case (q8), seven intravitreal injections and seven follow-up visits would be required.

Aflibercept 8 mg is a new, higher concentration formulation that offers enhanced stability and allows for the intravitreal administration of a dose that is four times higher than the 2 mg formulation. Due to aflibercept's strong binding affinity to VEGF and its estimated intravitreal half-life, this increased molar dose is expected to enable treatment intervals of up to 16 weeks following an initial phase of monthly treatments.[10] For its use, a loading dose of three monthly injections is recommended, followed by a treatment interval of no less than eight weeks. Following the same scheme illustrated earlier, the patient would undergo seven intravitreal injections in one year in case of a good response and eight intravitreal injections in one year in case of a poor response. In any case, two visits would be conducted in a year. In the second year of treatment, in the best possible scenario with the TriPla regimen, an additional three injections and one follow-up visit are needed, while in the worst case, six injections and two follow-up visits will be necessary.

For the T&E regimen, in the best case, two injections and two follow-up visits will be needed, while in the worst case, seven injections and seven follow-up visits will be required (Figure 2).

Brolucizumab is a single-chain antibody fragments (scFv) that represent the smallest functional unit of an antibody. Its compact size enables the delivery of a higher molar dose compared to larger antibody molecules, and it have the potential for more effective tissue penetration. These characteristics are intended to enhance the duration of its therapeutic effect.[11]

For its use, a loading dose of three-monthly injections or two/three injections every six weeks is recommended. Subsequently, it is necessary to maintain the minimum treatment interval above eight weeks. Thus, the patient, following the same scheme illustrated above for Faricimab, would receive the first injection of the second triplet after 8 weeks later the loading phase and the first follow-up visit after 28 weeks from the loading phase. Unlike Faricimab, since the loading dose includes only three injections, the patient would undergo seven injections and two follow-up visits in the first year. The use of this regimen with this drug should be carefully evaluated considering

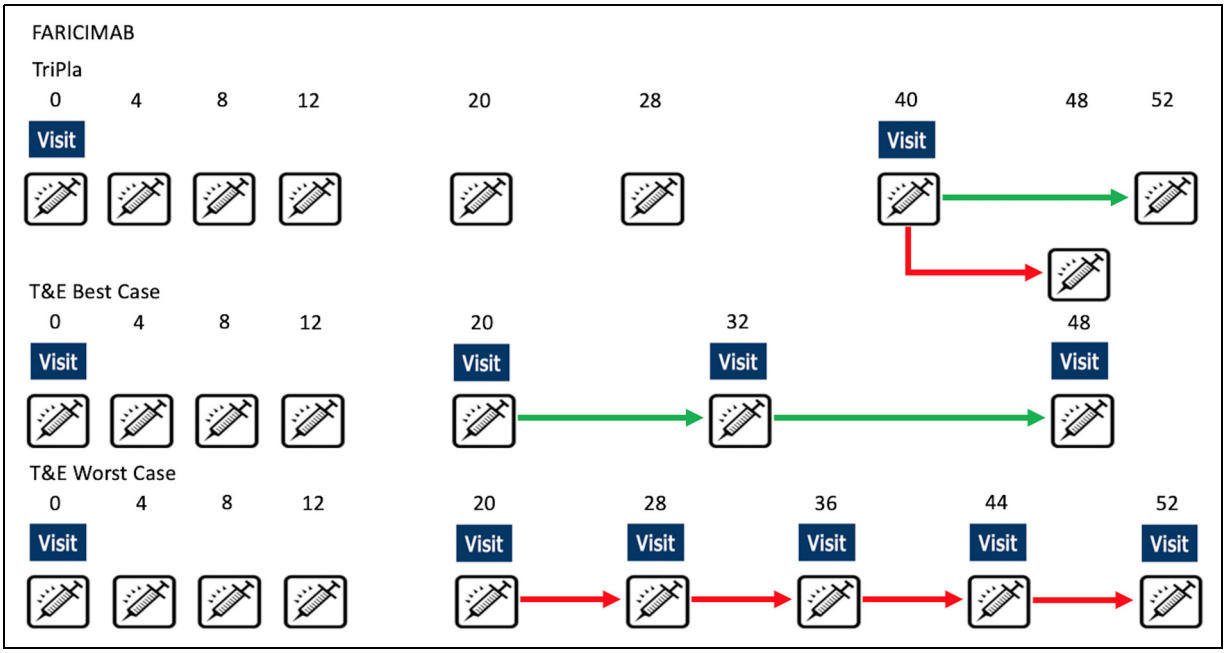

Figure 1. Illustrative treatment regimen with faricimab in the first 52 weeks of treatment. In the figure, from top to bottom, the TriPla regimen, the T&E regimen in the best case scenario, and the T&E regimen in the worst case scenario are shown. Where necessary for adjusting the treatment interval, the follow-up visit is indicated.

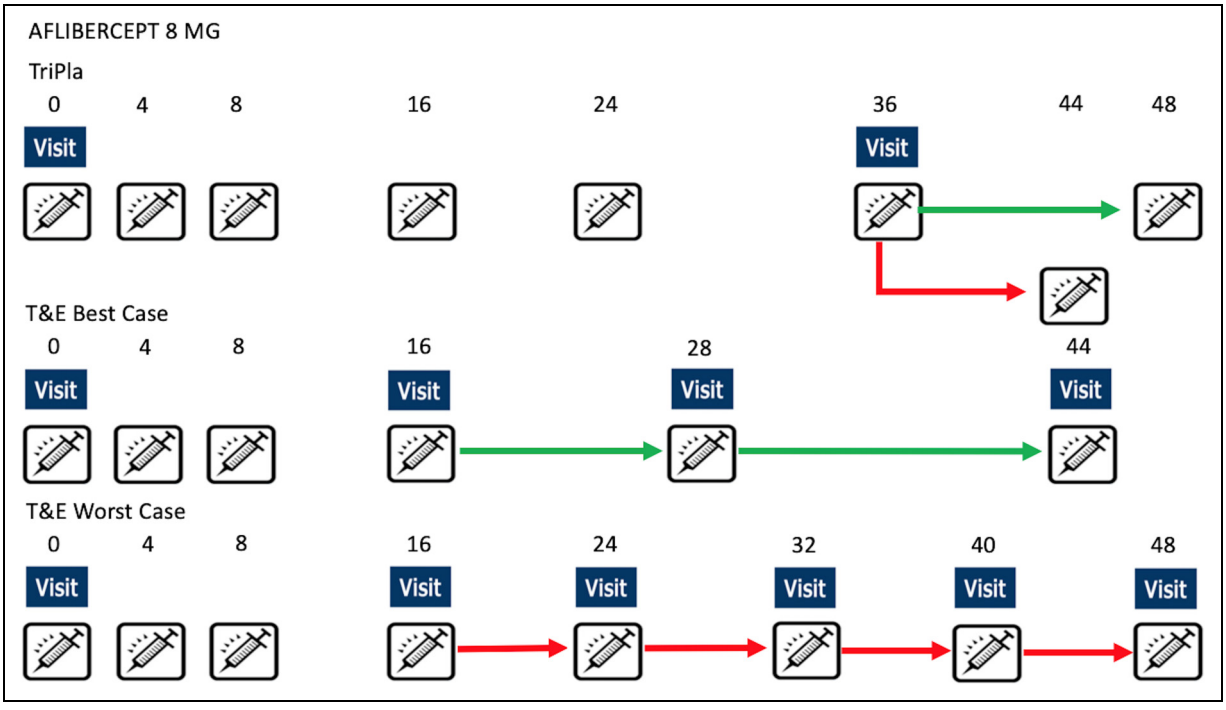

Figure 2. Same illustration for aflibercept 8 mg.

the higher risks of intraocular adverse events, despite the actual prevalence of these still being debated. Considering a loading phase with a 6-week interval, in the second year of treatment, the number of injections is comparable to those required for Faricimab. However, if we consider a loading dose with injections every four

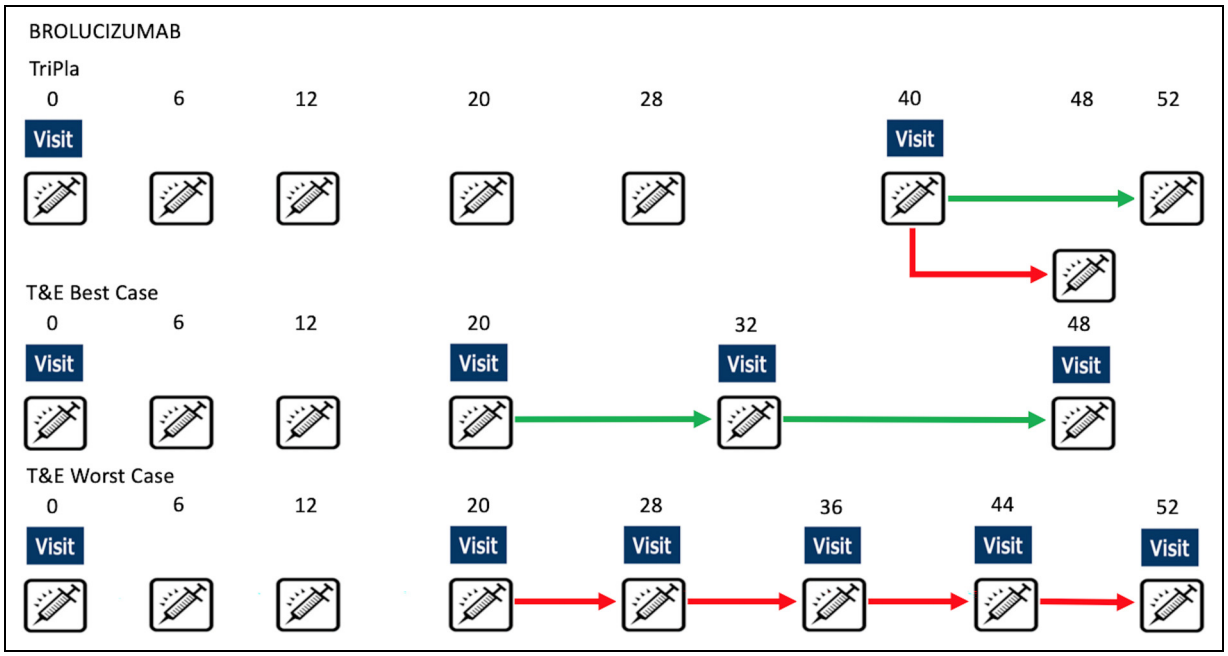

Figure 3. Illustration for brolucizumab. In the case of choosing to perform a loading phase of 3 monthly injections, the scheme of treatment for all the regimens become comparable to those shown for Aflibercept 8 mg in Figure 2.

weeks, the numbers of injections required during the second year of treatment are comparable to Aflibercept 8 mg (Figure 3).

Patients currently treated with the T&E regimen using new Anti-VEGF drugs require between 8 and 15 intravitreal injections over the first two years of treatment, with the number of visits ranging from 6 to 13 (Table 1).

Patients managed with the TriPla regimen require between 10 and 13 injections but only 3 to 4 visits. Obviously, if the response to the treatment is unsatisfactory after the initial injections, it would be advisable to opt for a therapeutic switch or reconsider the diagnosis.

Frequent clinical visits for intravitreal injections can significantly impact the quality of life for patients with AMD. Studies report that approximately 40% of patients undergoing anti-VEGF treatment experience moderate to severe difficulty in managing their daily activities due to frequent clinic visits (2). Challenges such as arranging transportation, taking time off work, and the psychological toll of recurrent treatments contribute to treatment fatigue and potential non-adherence (6). By reducing the number of visits to 3–4 annually compared to the 6–13 visits typical in the T&E regimen (7), the TriPla regimen alleviates these burdens. This streamlined approach is particularly beneficial for elderly or mobility-restricted patients, enhancing overall satisfaction with care.

The economic implications of the TriPla regimen are substantial. The T&E regimen typically requires 6–13 annual visits, resulting in a cumulative cost of $6,000–$12,000 per year per patient in direct healthcare expenses (5). In contrast, the TriPla regimen, requiring only 3–4 visits, reduces costs by 30–40% due to fewer clinic visits and lower administrative overhead (8). A recent cost-analysis study demonstrated that reducing clinic visits by even 20% leads to significant annual savings for national healthcare systems, estimated at over $300 million in countries with a high AMD prevalence, such as the United States (4). Furthermore, fewer visits translate into reduced patient-related expenses, including transportation

Table 1. The table shows the number of injections and visits required from the two regimens (TriPla and T&E) with new anti-VEGF agents in the first 104 weeks of treatment. For Brolucizumab is considered a loading phase of one injection every 6 weeks.

Treatment Regimen (0–104 week	Injections	Visits
Faricimab TriPla Best	11	3
Faricimab TriPla Worst	13	4
Faricimab T&E Best	9	6
Faricimab T&E Worst	15	12
Aflibercept 8 mg TriPla Best	10	3
Aflibercept 8 mg TriPla Worst	13	4
Aflibercept 8 mg T&E Best	8	6
Aflibercept 8 mg T&E Worst	15	13
Brolucizumab TriPla Best	10	3
Brolucizumab TriPla Worst	12	4
Brolucizumab T&E Best	8	6
Brolucizumab T&E Worst	14	12

and lost workdays, easing financial burdens on individuals and caregivers.

Despite its advantages, the TriPla regimen has some limitations. The fixed triplet structure may not suit all patients, particularly those with highly variable responses to treatment. A retrospective study of AMD patients indicated that approximately 20% required more frequent monitoring than standard regimens to avoid disease progression (7). Additionally, logistical challenges in scheduling three consecutive injections in busy clinics may lead to delays, potentially impacting treatment outcomes. These limitations emphasize the importance of careful patient selection and flexible implementation strategies when adopting the TriPla regimen.

Implementing the TriPla regimen in daily clinical practice necessitates streamlined workflows and robust communication between providers and patients. A recent survey of retinal specialists highlighted that 75% found fixed scheduling models like TriPla feasible when supported by adequate staff and resources (8). Telemedicine and home-monitoring tools, such as handheld optical coherence tomography (OCT) devices, could enhance the regimen by minimizing unnecessary visits (9). For instance, the use of OCT for remote disease activity monitoring reduced in-office visits by 15% in a pilot study while maintaining equivalent visual outcomes (10). Adoption of these technologies, combined with flexible scheduling protocols, can optimize TriPla implementation in diverse healthcare settings.

The TriPla treatment approach, which may require a slightly higher number of injections in the first two years of treatment, would allow for a reduction in the number of necessary visits and improve the scheduling of the centers providing this service. This would allow patients to receive an adequate number of intravitreal injections while reducing the workload on specialists.

Conclusions

Thanks to the introduction of new drugs for the treatment of exudative AMD and new treatment regimens, it is possible to provide adequate service to the patient's needs reducing the burden of specialists, hospital facilities and national health services.

Authors' note

Giuseppe Querques confirms that he is an associate editor of this journal and was not involved in the peer review process for this paper.

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