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TriPla Regimen: A new treatment approach for patients with neovascular age-related macular degeneration in the COVID-19 "era"

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Abstract

In the last months, a rapidly increasing number of people have been infected with severe acute respiratory syndrome coronavirus 2, the virus causing coronavirus disease 2019 (COVID-19). Due to the risk of cross-infections, the number of visits and injections was dramatically reduced in the last months, and the time between visits has been rescheduled from every 15 to 45 min, significantly impairing the total number of available visits. Although continuity of care has been allowed, a series of measures to diminish the risk of contamination need to be adopted until the end of this pandemic outbreak, which may persist until the development of an effective vaccine. For these reasons, we have introduced a new treatment regimen that is aimed at reducing the number of in-person visits and achieving continuity of treatment. This regimen is named "Triple and Plan" (TriPla). The main advantage of the TriPla regimen is to reduce the number of visits of patients in comparison to the pro re nata and treat and extend regimen. Using the TriPla regimen, the risk of contamination would be reduced. Furthermore, by reducing the number of scheduled visits, physicians could guarantee an adequate number of examinations for each patient, lengthening the interval between visits, and reducing the risk of cross-infections.

Keywords

RETINA, age-related macular degeneration, techniques of retinal examination, retina - medical therapies, retinal pathology/research

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Age-related macular degeneration (AMD) is the most important cause of vision loss in Western counties.[1,2] AMD may be classified in two different forms – that is, neovascular and non-neovascular AMD – based on the presence of macular neovascularization (MNV).

Exudative neovascular AMD (nAMD) is mainly treated with repeated intravitreal anti-vascular endothelial growth factor (VEGF) injections. Importantly, the annual number of anti-VEGF injections is strictly associated with functional and anatomical outcomes in patients affected by nAMD. In detail, an higher frequency of examinations and injections is associated with a greater best-corrected visual acuity (BCVA) gain and, above all, maintenance of the gain over the time.[3] Holz and associates[3] reported that, in a real-life setting, patients received fewer anti-VEGF injections as compared to clinal trials, resulting in a lower BCVA gain. In detail, they analyzed 1184 nAMD patients

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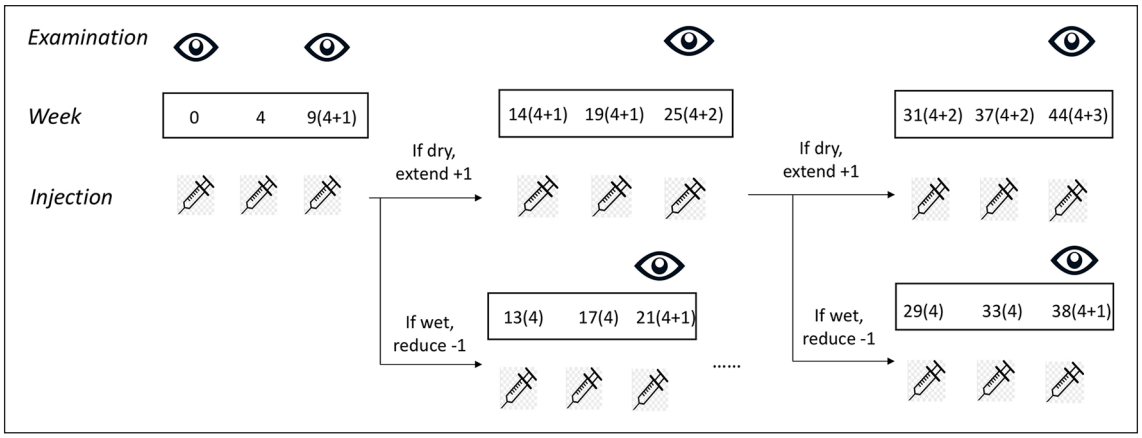

Figure 1. The proposed "Triple and Plan" (TriPla) regimen for the treatment of neovascular age-related macular degeneration (nAMD) in the COVID-19 era.

Both treatment-naïve and previous-treated patients returning after COVID-19-related spontaneous interruption of injections patients are evaluated at week 0 and three injections are scheduled with an interval of 4 weeks between the first and second one, and 5 weeks between the second and third one. Before the third injection (week 9), the physician performs a new evaluation in order to plan the next triple treatment. If the macula is dry, the interval between injections is lengthened of 1 week (+1 week). Thus, the new three injections are scheduled with 5 weeks between the third and fourth injection, 5 weeks between the fourth and fifth injection, and 6 weeks between the fifth and sixth injection (5-5-6). On the other hand, if at the revaluation the macula is wet, the interval of injections should be reduced of 1 week (–1 week), with a minimum interval of 4-4-5 weeks between the three planned injections. This treatment scheme should be applied to all triple injections.

with a 2-year follow-up and demonstrated that the average number of injections was 7.2 (5.0 injections in the first year and 2.2 injections in the second year) with a BCVA gain of +2.4 letters at the end of the first year and only +0.6 letters at the end of the second year of follow-up.[3] These numbers significantly differ with those from clinical trials, which were overall characterized by greater average values. In the CATT study, the mean BCVA gain was between +5.0 and +6.7 letters at the 2-year follow-up for the "as-needed" zero tolerance groups, which were treated with either bevacizumab or ranibizumab injections. Similarly, the average number of injections was 14.1 and 12.6 for the two study groups after 2 years of follow-up.[4,5]

In the last few months, a rapidly increasing number of people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19).[6] The COVID-19 pandemic has been spreading worldwide and the Italian outbreak represents one of the largest outside China.[7] Due to the COVID-19 spread, the Italian population has been quarantined from March 9th, 2020 to May 3rd, 2020. Although continuity of care has been allowed, a series of measures to diminish the risk of contamination for both healthcare workers and patients have been adopted and may be kept until the end of this pandemic outbreak, which may persist until the development of an effective vaccine. As an example, each visit has been rescheduled from every 15 min (before the COVID-19 pandemic) to 45 min, this significantly impairing the total number of available visits.[8,9] As a consequence, the number of available slots for visits may not be enough to achieve continuity of care for all patients with retinal diseases.

Furthermore, from September 2019, in several administrative Italian regions, including Lombardy, off-label bevacizumab has become the only reimbursable drug for the treatment of nAMD. However, assuming that previous reports have demonstrated that bevacizumab injections are less effective in terms of duration and anatomical effects as compared to ranibizumab and aflibercept on-label injections,[10,11] the total number of intravitreal injections for nAMD has significantly increased in the last months in our unit (unpublished data).

Monthly intravitreal injections are not applicable in the clinical practice due to the significant treatment burden for patients, caregivers, and physicians.[3] Conversely, pro re nata (PRN) regimen and treat and extend (T&E) regimen need an elevated number of examinations and accesses to hospitals,[11,12] which may be difficult to be accomplished during the COVID-19 pandemic. In contrast with in-person visits, which may be at high risk of contamination, intravitreal injections, in Italy, are performed in an operating room with laminar flow, this significantly reducing the number of infective organisms in the theater air and thus the risk of cross-infections.

For all the reasons explained above, we introduced a new treatment regimen which is aimed at reducing the number of in-person visits and achieving continuity of treatment. This regimen is named "Triple and Plan" (TriPla). The TriPla regimen has three main objectives: (i) ensuring a suitable number of injections during the COVID-19 era, (ii) reducing the number of accesses of patients in the visiting rooms, and (iii) lowering the congestion in the waiting rooms. The TriPla regimen relies on one examination every three injections (Figure 1). In detail, after the first examination, both

treatment-naïve and previous-treated patients returning after COVID-19-related spontaneous interruption of injections are re-scheduled to three consecutive injections ("Triple") and to the revaluation (including complete ophthalmic examination, best-corrected visual acuity measurement, and optical coherence tomography examination) before the third injection. The three injections are scheduled with an interval of 4 weeks between the first and second one, and 5 weeks between the second and third one. If at the 9-week revaluation the macula is dry [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 interval of injections should be lengthened of 1 week (+1w). So, another course of three injections should be planned (5 weeks between the third and fourth injection, 5 weeks between the fourth and fifth injection, and 6 weeks between the fifth and sixth injection [5-5-6]) with the revaluation before the sixth injection. On the other hand, if at the revaluation the macula is wet [i.e. presence of sub- and/or intra-retinal hyporeflective exudation or subretinal hyperreflective material (SHRM) using structural optical coherence tomography or hemorrhages at fundus examination], the interval of injections should be reduced of 1 week (-1w), with a minimum interval of 4-4-5 weeks between the three planned injections (Figure 1). As per protocol, the maximum lengthening of interval between injections could be planned to 8 (4+4) weeks.

The first advantage of the TriPla regimen is to reduce the number of visits of patients in comparison to the PRN and T&E regimens. With this approach, the risk of contamination would be reduced. Furthermore, by reducing the number of scheduled visits, physicians could guarantee an adequate number of examinations for each patient, lengthening the interval between visits at 45 min and reducing the congestion within the waiting rooms.

The second advantage of the TriPla regimen is to maximize the number of treatments in nAMD patients, compensating for the shorter duration of the bevacizumab treatment in comparison to other anti-VEGF available molecules, in particular with aflibercept injections. In fact, this protocol could be adapted also for ranibizumab injections due to the similarity of injection's intervals of bevacizumab and ranibizumab.

A limitation of the TriPla regimen is secondary to the smaller number of visits, which may result in missing relapses that could benefit of an interval shortening before the end of the three consecutive injections. Also, the development of exudative nAMD in the fellow eye may also be missed.

In conclusion, we proposed a novel anti-VEGF regimen that may be particularly useful during the COVID-19 pandemic, in order to minimize the access of nAMD patients in the ophthalmic units and, at the same time, maintain an appropriate number of injections. We will keep adapting our clinical activity to this rapidly evolving situation, by balancing continuity of care for nAMD patients with risks of COVID-19 contamination.

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.

Declaration of conflicting interests

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