



Rational Treatment of Exudative AMD: The Case for Standardised Practice: "Know-and-Treat"

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Editorial

The treatment of exudative Age-related macular degeneration (AMD) has been revolutionised over the last ten years with the introduction of anti-vascular endothelial growth factor agents (anti-VEGF).

The initial treatment regimen recommending injections at fixed intervals as per the pivotal registration studies [1-3] for Ranibizumab or Aflibercept, have been confronted with real-life clinical practice and progressively modified based on this experience. Furthermore, the results of additional studies have led to changes being made to the Marketing Authorisation, in particular for ranibizumab. The emergence of the notion of a personalised treatment regimen based on the individual patient, the type of choroidal neo-vessel, and the physician's experience has resulted in a multitude of different treatment regimens not all of which can be applied by practitioners, thus creating a very confusing situation.

It would appear advisable to determine the most consensual anti-VEGF treatment regimen possible, with a view to simplifying the situation. This regimen needs to be based on both clinical experience and the data from undisputed clinical trials.

If this standard treatment regimen is widely shared, it will not limit our thinking and practices, but rather will create broader cohesion across our specialty and confirm the rigour and rationality of our clinical practice. It will allow us to consolidate our expertise based on best practice and reinforce our commitment to controlling costs through decisions based on sound evidence.

We propose a tailor-made treatment regimen, which we have called "Know-and-Treat" (Figure 1). This regimen systematically includes:

- An induction period during which at least three anti-VEGF intravitreal injections (IVI) administered at one-month intervals (until no sign of exudation on OCT).
- A follow-up and familiarisation period with monthly follow-up visits under a Pro Re Nata (PRN) regimen lasting several months.
- A personalised maintenance phase under a Treat-and-extend regimen introduced between months 6-9, depending on the time to recurrence after the end of the induction phase.

Naturally, this regimen leaves the physician entirely free to make adjustments in the event of treatment failure, using phases during which treatment is stepped up such as reinforced PRN, or by switching or switching the treatment back.

Why is this Induction Phase of Three IVT Over at Least Three Months a Vital Prerequisite?

The results of the registration studies for the use of ranibizumab for AMD (MARINA and ANCHOR) [1-2] show that the induction phase procures a rapid increase in visual acuity which subsequently changes very little. This initial gain in visual acuity, obtained with each injection, was also reported in a phase III study (HARBOR) [4] of ranibizumab. Real-life studies such as the French retrospective observational study LUMIERE [5] have confirmed the importance of this induction phase showing that patients who undergo a 3-month induction phase have a higher increase in visual acuity. The recent results from the LUMINOUS study, a 5-year observational study including 30,000 patients, presented at ARVO [6], also found a higher gain in visual acuity at 1 year for the

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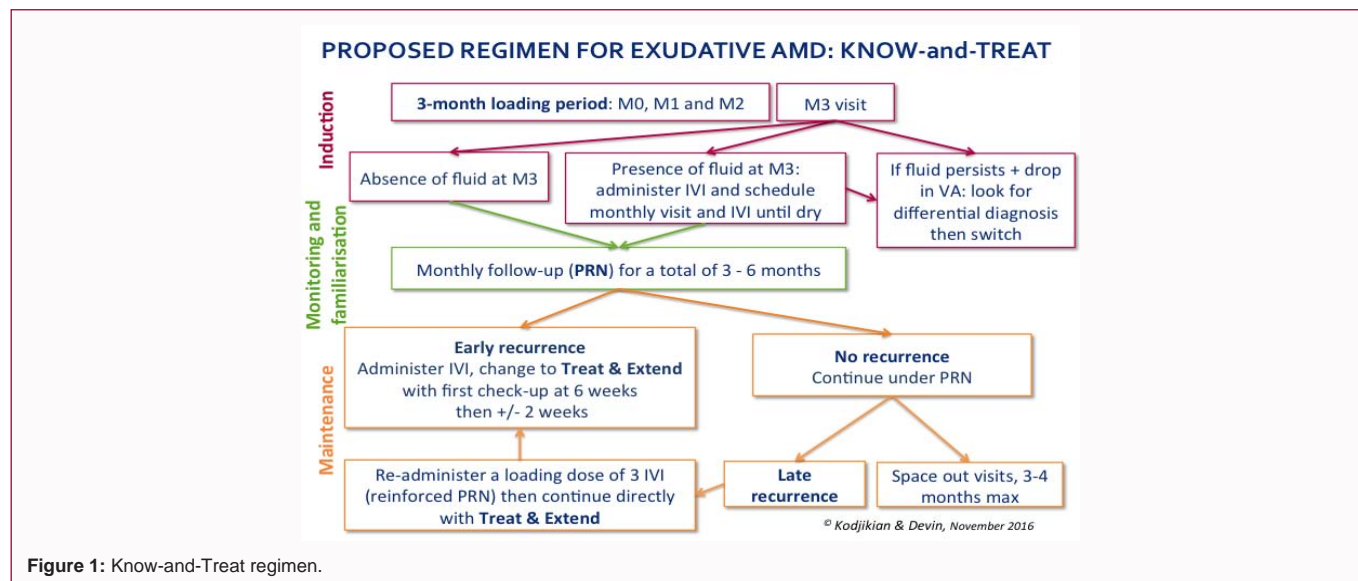
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sub-group of patients who received a 3 IVI induction phase.

Why Recommending a Monitoring Phase with Monthly Follow-up and Treatment on a PRN Basis, After the Induction Phase?

The French GEFAL study [7] showed that around 20% of patients only required the first three IVI over the course of a one-year monthly prospective follow-up period. Retrospective, multi-centre, observational studies (the Australian Fight Retinal Blindness observational registry) [8] have shown complete neovascular inactivation in 61.1% of patients following their initial treatment with 1 to 3 IVI. This percentage increased to 80% after 9 months of treatment.

Furthermore, the PRONTO study [9] was the first to prove the effectiveness of the PRN regimen as of the first year of treatment with ranibizumab, with the criteria for retreatment based on the OCT and visual acuity (average gain of 11.1 letters at 24 months, for a mean number of 9.9 injections; 43% of patients gained over 15 letters at 24 months). The results of this study also highlighted the large differences in the number of injections required from one patient to another, demonstrating the importance of individualised treatment plans. The HARBOR study also did not find any clinically significant difference between a PRN and a monthly regimen at 12 months and found that the gain in visual acuity was maintained at 24 months (patients received a mean of 13 IVI over a 2-years period for a mean gain in visual acuity of +7.9 letters with a mean time lapse between IVI of 9.9 weeks, after the induction phase; 93% of patients did not require monthly treatment over the 2-year period). Once again, these results confirm the benefit of an individualised treatment regimen.

Nonetheless, the independent study CATT [10] found the PRN regimen to be statistically inferior by 2 letters, when compared with the monthly regimen at 2 years, both for the ranibizumab and the bevacizumab groups. This was confirmed in the meta-analysis of the CATT and IVAN studies [11], which again found a difference of over 2 letters, with a confidence interval of -0.5 letters to almost -4.0 letters.

Therefore, although a PRN regimen can be considered, it will procure a lower increase in visual acuity than a recurrence-anticipating treatment regimen (such as treat-and-extend). It does however offer a number of benefits, and it therefore seems wise for

the regimen to include a PRN treatment phase. However, in the event of recurrence this phase should be kept short.

One of the main benefits of the PRN regimen is that it allows us to identify the minority of patients (sometimes referred to as the happy few) requiring very few IVI, and to assess the frequency of recurrence. A small case series study by Horster R et al. [12] evidenced regular recurrence in 76% of patients (at least 2 recurrences < 50 days) and irregular recurrence in 24% of patients (>50 days). The findings of another small case series published by Mantel I et al. [13] also support the predictability of recurrence intervals in any given patient.

The high inter-individual variability in these recurrence intervals argues in favour of the need for individualised treatment plans and for a PRN phase after the induction phase.

Why is it Important to Keep the PRN Phase Short?

In the GEFAL study, 80% of patients who required a 4th IVI received it within the 3 months following the end of the induction phase. Furthermore, 87% of patients who received a 4th IVI required a 5th injection or more. The PRN phase following the induction phase should therefore be kept short, between 3 to 6 months, in the event of early recurrence. After this transitional phase, we recommend adopting a recurrence-anticipating regimen.

Moreover, the analysis of the results of a recent retrospective study conducted by Hatz and co-workers [14], assessing the effect of the change in treatment regimen from PRN to treat-and-extend, suggests that for the same molecule, the treat-and-extend regimen offers improved anatomical and functional outcomes. This change in regimen means patients receive more intensification IVI treatment. Transferring patients whose AMD is not properly controlled under the PRN regimen to a treat-and-extend regimen offers improved functional and anatomical results with less follow-up visits against the inconvenience of a greater number of annual injections.

What is the Optimal Maintenance Phase for AMD Patients after the PRN Monitoring Phase?

In the second paragraph, we explained why a recurrence-

anticipating regimen is superior in the long term to a PRN treatment regimen.

Treat-and- extend is an excellent treatment regimen to introduce once the physician is familiar with the patient and their neovessels. The LUCAS study investigating a treat-and-extend protocol over a two-year period confirmed its effectiveness [15]. The gain in visual acuity in the first year is maintained in the second year. Similar results have been obtained in a number of observational studies of treat-and-extend.

A switch between molecules should definitely be considered if there is an increase in exudation with a reduction in visual acuity after the induction phase. In other cases, to be sure not to overlook late responders, it is recommended that at least six IVI of the same molecule are administered before any decision to switch is made. Furthermore, a switch back to the original molecule should only be considered after using the alternative molecule for a sufficient length of time (six IVI) [16].

We propose a standard treatment plan with the aim of simplifying and harmonising the treatment of exudative AMD. However, in some cases this plan will of course need to be adjusted. It is important to remember that fixed regimens, regardless of whether they are monthly or every two months give excellent results that are extremely useful for managing aggressive choroidal neovessels and monocular patients. In the same way abandoning the treat-and-extend regimen in favour of a PRN regimen is a good choice for patients who develop AMD in the second eye during the treatment of one eye. Furthermore, for patients who do not receive regular injections and experience a late recurrence, i.e. at a significant interval since the last IVI, we recommend a reinforced PRN regimen (treatment with two or rather three successive IVI), which in fact corresponds to a further induction phase, before directly moving on to a treat-and-extend regimen.

After 6 months' neovascular remission under the treat-and-extend regimen it is very difficult to make any recommendations. In any case, it is vital that all patients are followed up every 3-4 months throughout their lives.

In short, the treatment of choroidal neovessels in exudative AMD could be optimised with a simple treatment regimen based on the latest scientific advances. This treatment plan entitled Know-and-treat includes:

- An induction phase for all patients.
- A monitoring and familiarisation phase with monthly follow-up under a PRN regimen for a duration of three to six months.
- An individualised maintenance phase under a treat-and-extend regimen in months 6-9.

This plan offers patients individualised treatment, which is vitally important to ensure their exudative AMD is neither over- nor under-treated. Furthermore, it provides a structured framework, which will make it easier in the future to integrate new potential molecules in addition to anti-VEGF.

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