Extended Loading Dose of Anti-VEGF Treatment in Diabetic Macular Edema Patients: A Cost-Consequence Analysis

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BACKGROUND

- Diabetic macular edema (DME) is a frequent retinal complication in diabetic patients that has become the major cause of loss of visual acuity in these patients, with an increasing incidence and annual mean rates over 2-3% depending on the type of diabetes[1].
- In current clinical practice in Spain, for the management of center-involved DME patients, most of the specialists (96.4%) selected an induction treatment of monthly anti-VEGF injections for a period of between 3 to 6 months as the first treatment administered[2,3].

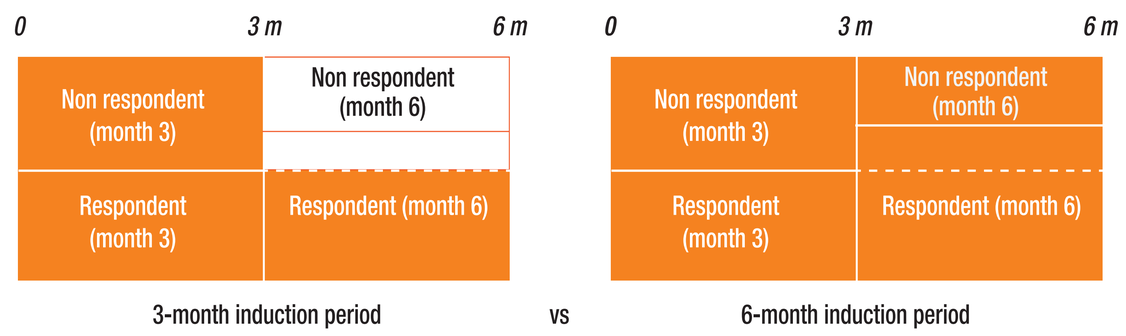
OBJECTIVE

To assess the clinical and economic consequences of an extension of the loading dose of anti-VEGF treatments from 3 to 6 monthly injections in patients with persistent central involved diabetic macular edema (DME) and visual impairment in Spain, based on the findings of Protocol T subanalysis regarding the treatments considered.

METHODS

- A cost-consequence model was developed in Microsoft Excel to analyzed the economic and clinical implications of treating non-respondent DME patients beyond the established 3-month induction period by extending the loading dose up to 6 months of three anti-VEGF treatments **(Figure 1).**

Figure 1. Induction periods considered in the cost-consequence analysis



Blue-colored areas indicate the treated patients within each period.

- The anti-VEGF treatments included in the analysis were aflibercept, ranibizumab and bevacizumab.
- From a National Health System perspective, this analysis estimated the pharmaceutical treatment costs, considering the ex-factory unit prices (€, 2019)[4]:
  – **Aflibercept 40 mg/ml 1 vial**: €742 per vial
  – **Ranibizumab 10 mg/ml 1 vial**: €742 per vial/syringe
  – **Bevacizumab 25 mg/ml 1 vial 4 ml**: €341.71 per vial.
- The study protocol required a monthly administration of intravitreal injections for all treatments.
- Response and non-response rates in persistent DME patients at 3 and 6 months were obtained from the Protocol T post-hoc analysis **(Table 1)**. This subanalysis assessed the prevalence of persistent central-involved DME every 4 weeks during a 24-week period[5].
- Treatment response was considered as a reduction on central subfield thickness (CST) under 250 µm.
- In line with Protocol T study, a total of 546 patients was considered in the present analysis (aflibercept, 190; ranibizumab, 176; bevacizumab, 180)[5].

Table 1. Persistent diabetic macular edema through 3 and 6 months

Patients with persistent DME	Month 3 (week 12) (n/N, %)	Month 6 (week 24) (n/N; %)
Aflibercept	95/187 (50.80%)	60/190 (31.58%)
Ranibizumab	91/171 (53.22%)	73/176 (41.48%)
Bevacizumab	129/177 (72.88%)	118/180 (65.56%)

At 24 weeks, p<0.001 for aflibercept vs bevacizumab, p=0.05 for aflibercept vs ranibizumab and p<0.001 for ranibizumab vs bevacizumab.
Source: Protocol T post-hoc analysis (Bressler NM, et al. JAMA Ophthalmol. 2018;136(3):257-69).

- The percentage of patients with response in each period (3 and 6 months) were applied to estimate the number of treated patients with response with each therapy for both time points.
- The number of additional injections (and vials) administered to 3-month non respondent patients was estimated from week 12 to week 24 within the 6-month treatment period of Protocol T study.
- The costs of incremental anti-VEGF treatment between the extension of the loading dose to 6 months and the established 3-month treatment for a 6-month period were calculated.
- Finally, the incremental anti-VEGF treatment cost per additional respondent patient at 6 months was assessed for each treatment.

RESULTS

- The percentage of patients with response at 3 months were 49.20% (93 patients), 46.78% (82 patients) and 27.12% (49 patients) with aflibercept, ranibizumab and bevacizumab, respectively. At 6 months, the rates increased to 68.42% (130 patients), 58.52% (103 patients) and 34.44% (62 patients), respectively.
- The total number of extended injections (months 3 to 6) used in patients with persistent DME at month 6 was 180, 219 and 354 for aflibercept, ranibizumab and bevacizumab, respectively **(Table 2)**.

Table 2. Number of additional injections (from month 3 to 6) in 3-month non-respondent patients based on the response at 6 months

3-month induction vs 6-month induction	Additional injections in 6-month respondent patients*	Additional injections in 6-month non-respondent patients*	Total additional injections*
Aflibercept	110	180	290
Ranibizumab	62	219	281
Bevacizumab	40	354	394

*All figures related to injections were rounded to the nearest whole number. However, estimations used the exact figures obtained from each response rate and cohort size.

- Extending the **loading dose** to non-respondent patients would mean a cost of €214,862.57 to obtain 37 additional respondent aflibercept patients, and €208,488.98 and €134,483.16 for the 21 and 13 additional respondent patients with ranibizumab and bevacizumab **(Table 3)**.

Table 3. Additional respondent patients, injections and incremental costs (3-month induction vs 6-month induction)

3-month induction vs 6-month induction	Additional respondent patients*	Additional injections*	Incremental treatment costs
Aflibercept	37	290	€214,862.57
Ranibizumab	21	281	€208,488.98
Bevacizumab	13	394	€134,483.16
TOTAL	70	964	€557,834.71

*All figures related to patients and injections were rounded to the nearest whole number. However, estimations used the exact figures obtained from each response rate and cohort size.

- In this study, an extended **loading dose** up to 6 months would imply incremental costs of anti-VEGF treatment per additional patient with response (3-month non-respondent and 6-month respondent) of:
  – **€5,882.77 (8 injections)** [aflibercept]
  – **€10,091.03 (14 injections)** [ranibizumab]
  – **€10,198.59 (30 injections)** [bevacizumab]
- For the total of the patients treated with anti-VEGF on average **€7,927.02 (14 injections)** per **additional respondent** patient would be needed.

CONCLUSION

- **Considering the evidence of response of treatment on persistent DME from the Protocol T post-hoc analysis, the extension of the loading dose to a 6-month induction period (from 3 to 6 monthly injections) means that it would be necessary to invest from €5,883 to €10,199 per additional respondent patient (3-month non-respondent and 6-month respondent)**
- **The potential benefits of extending the current treatment and its economic implications would allow clinicians and other stakeholders to make informed decisions of whether to extend treatment or switch to alternative options.**

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