Time Dependence and Cumulative Exposure of Intravitreal Anti-VEGF

Treatment for Diabetic Macular Edema on Subsequent Development of Proliferative Diabetic Retinopathy

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Purpose : The effect of the timing and cumulative exposure of repeated anti-vascular endothelial growth factor (VEGF) injections for treatment of diabetic macular edema (DME) on the subsequent risk of proliferative diabetic retinopathy (PDR) is unclear. We report associations for PDR development on patients receiving anti-VEGF treatment for DME at point of care and evaluated the application of the novel weighted cumulative exposure (WCE) method to such data.

Methods : Retrospective multicenter electronic medical records-based study from 27 centers across the United Kingdom. We implemented (1) a multivariable Cox model ignoring anti-VEGF exposures as baseline (MCox), and modelled the complex time-varying nature of repeated anti-VEGF injections using 3 more models as: (2) a time-dependent unweighted cumulative sum of exposures (MtdcCox), (3) as the average anti-VEGF injections over the most recent 6 months (M6moCox), and (4) as a the weighted cumulative sum of past exposures (MWCE). Primary outcome measure was PDR development. All models allowed for baseline diabetic retinopathy (DR) grade, age, sex, ethnicity, type of diabetes and index of multiple deprivation. Model goodness of fit was quantified by Akaike information criterion (AIC).

Results : We included 4439 patients. The unweighted time-dependent multivariable Cox regression (MtdcCox AIC=3454; M6moCox AIC=3452) provided a better model fit than the baseline model (MCox AIC=3488), and the MWCE had the best fit overall (AIC=3364). Table 1 shows hazard ratios for all models. Severe NPDR showed a more than 5-fold increase in hazards of PDR when compared to mild NPDR ($p<0.0001$) in all models. Every 5-year rise in age was associated with decreased hazards of PDR in all models ($p<0.001$). In MWCE, patients with type 1 diabetes had a 2.02-fold increase in PDR hazards ($p=0.0001$), when compared with type 2 diabetes. The least deprived patients showed a 38 to 42% reduction in PDR hazards when compared to the most deprived patients in all models ($p<0.048$)

Conclusions : Baseline DR features remain the most important predictor for clinical outcomes but, our model highlighted the importance of adjusting for anti-VEGF injection number and timing that is achievable in this novel application of the WCE model to ophthalmology data. WCE models can enhance our interpretation of complex time series data.