# Author Response: Does the Fc Region Have a Role in the Ocular Half-Life After Intravitreal Injection?

We thank Caruso et al. for their insightful comment regarding our article.[1] They pointed out the methodological issues and presented the re-analyzed result using the data in our article (Table 1).[2] In our article, using compartmental analysis, we showed that the absence of fc region (Fcf VEGF-Trap) extended the half-lives in the vitreous and retina/choroid (145.02 and 101.12 hours, respectively) compared to those of VEGF-Trap (103.99 and 44.42 hours, respectively). However, Caruso et al. showed that the difference in vitreous half-life became insignificant when it was re-analyzed using the noncompartmental analysis method and the retina/choroid half-life of VEGF-Trap could not be calculated. Thus, we also re-analyzed our data using the noncompartmental analysis method and confirmed the same result of half-lives as calculated by Caruso et al. The results from noncompartmental analysis and compartmental analysis can be interpreted differently because the two analysis methods have different concepts of estimating the PK parameters. Noncompartmental analyses do not assume compartments and is usually less complex than compartmental method, whereas compartmental analysis considers the complex system of a certain number of compartments, which may be actual physical organs/tissues.[3,4] This approach may result in potential variability in the outcomes of the analysis and the interpretation. In addition, compartmental models can be applied to population analysis.[5] In this study, we used the compartmental analysis method because it was considered to better reflect the physiological compartments of the eye (vitreous, retina, and anterior chamber), and each concentration value was collected from a different individual, being close to sparse data from a population. We think the discrepancy between the results from the noncompartmental analysis and compartmental analysis might have been originated from the insufficient data points and small sample size in our study. We consider this may be overcome by a larger amount of data, including sample size for each time point and the number of sampling points in future studies.

The effect of the Fc region on ocular pharmacokinetics might seem confusing as the difference of half-lives are varying by the two analysis methods. However, considering the smaller molecular weight of the FcF VEGF-Trap (100 kD) than VEGF-Trap (145 kD), even the comparable vitreous half-lives of the two molecules obtained from the noncompartmental analysis indicate the extension of the vitreous half-life by the absence of Fc region. However, to our thought, the effect of half-life extension by the absence of Fc region is only modest and it may not be enough to change the therapeutic paradigm of the current ophthalmic anti-VEGF drugs. In other words, the Fc region should be considered as one of the factors affecting ocular pharmacokinetics, rather than a major determinant, such as molecular weight.[6] However, in the development of new ophthalmic antibody drugs, the effect of Fc region may be one of the considerations in terms of controlling ocular pharmacokinetics and reducing the potential systemic exposure.

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