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COMMENT

Globe size and bevacizumab treatment in retinopathy of prematurity: should we adjust the dose?

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Bevacizumab, a biological agent targeted against vascular endothelial growth factor, is an increasingly popular treatment for retinopathy of prematurity (ROP). The effectiveness of this treatment has been confirmed with a randomized controlled trial,[1] but concern remains about potential systemic effects to the developing neonate. We put forward that it is possible to adjust the dose for smaller eyes, achieving the same intraocular concentration, but at the same time, reducing the total drug exposure to the child.

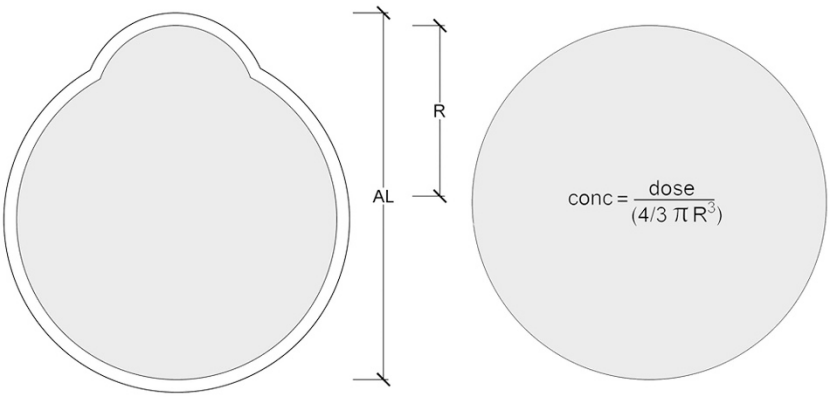
In a retrospective review of ROP, treated within our department with bevazicumab, we identified 11 babies that had axial length measurements performed (mean axial length 16.0 mm, SD ±0.6 mm, range 15.2–17.5 mm). We then used a mathematical model (Figure 1) to hypothesize what intravitreal concentrations would have been achieved for various globe sizes.

We hypothesize that the smallest eye in our series (15.2 mm) would achieve a concentration of 0.38 mg/ml, 19% more than the median eye (16.0 mm, concentration 0.32 mg/ml) and 58% more than our largest eye (17.5 mm, concentration 0.24 mg/ml). The largest eye treated in our series would have achieved an intravitreal concentration of 0.24 mg/ml, 25% less than the median eye, yet this patient still demonstrated involution of the ROP, highlighting that lower bevacizumab concentrations may still be effective in ROP.[2,3]

Despite a randomized controlled trial of bevacizumab in ROP, there is a paucity of information about the pharmacokinetics of bevacizumab in ROP.[2] There have been no dose finding studies and current doses are on the basis of a modification of the dose used for age-related macular degeneration.[4] Although bevacizumab is used for a different disease process in adults, it is interesting to note that even when half the adult dose is used, our model predicts higher concentrations in neonates than in adults (16.0 mm eye, 0.625 mg dose achieves 0.32 mg/ml concentration *vs* 23.5 mm eye, 1.25 mg dose achieves 0.2 mg/ml concentration).

The influence of globe size and intravitreal antiVEGF concentrations has been studied before in the adult population where, surprisingly, no effect could be identified.[5] Although no influence of globe size was found, their data contained many other variables such as different disease processes, lens status, drug reflux, and time points of aqueous sampling, which may have only been partly controlled for.

In the pediatric population, by using 0.625 mg rather than 1.25 mg, we are already, but only partially making an adjustment for globe size. Further adjustment on the basis of globe size is possible, either by dilution or adjustment of injection volume. Unfortunately, there are limitations to both methods. Dilution requires access to sterile facilities in addition to introducing the possibility of dilution errors, whereas adjusting the volume may not be practically possible. It is likely that injection volume can only be measured to the nearest 0.005 ml, so that an intended injection of 0.025 ml (0.625 mg of bevazicumab 25 mg/ml) varies anywhere from 0.02 to 0.03 ml. Despite these limitations, we suggest that in



axial length (mm)	Intraocular volume (ml)	concentration for 0.625mg dose (mg/ml)	concentration for 1.25mg dose (mg/ml)
15	1.60	0.39	0.78
15.5	1.77	0.35	0.71
16	1.95	0.32	0.64
16.5	2.14	0.29	0.58
17	2.35	0.27	0.53
17.5	2.57	0.24	0.49
18	2.81	0.22	0.45
18.5	3.05	0.20	0.41
19	3.32	0.19	0.38
19.5	3.59	0.17	0.35
20	3.88	0.16	0.32
20.5	4.19	0.15	0.30
21	4.51	0.14	0.28
21.5	4.85	0.13	0.26
22	5.20	0.12	0.24
22.5	5.58	0.11	0.22
23	5.96	0.10	0.21
23.5	6.37	0.10	0.20

Figure 1 Model used to calculate intraocular bevazicumab concentrations for 0.625 and 1.25 mg doses. Corneal thickness assumed to be 0.5 mm. AL, axial length; conc, concentration; R, radius.

eyes <15.6 mm axial length, the intended volume can be adjusted down to 0.02 ml and achieve the same desired intraocular concentration as found in the average sized ROP treated eye.

Conflict of interest

The authors declare no conflict of interest.

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