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Predicted biological activity of intravitreal VEGF Trap

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ABSTRACT

Aim: To compare the intravitreal binding activity of VEGF Trap with that of ranibizumab against vascular endothelial growth factor (VEGF) using a time-dependent and dose-dependent mathematical model.

Methods: Intravitreal half-lives and relative equimolar VEGF-binding activities of VEGF Trap and ranibizumab were incorporated into a first-order decay model. Time-dependent VEGF Trap activities (relative to ranibizumab) for different initial doses (0.5, 1.15, 2 and 4 mg) were calculated and plotted.

Results: Seventy-nine days after a single VEGF Trap (1.15 mg) injection, the intravitreal VEGF-binding activity would be comparable to ranibizumab at 30 days. After injection of 0.5, 2 and 4 mg VEGF Trap, the intravitreal VEGF-binding activities (comparable to ranibizumab at 30 days) would occur at 73, 83 and 87 days, respectively

Conclusion: On the basis of this mathematical model, VEGF Trap maintains significant intravitreal VEGF-binding activity for 10–12 weeks after a single injection.

Vascular endothelial growth factor (VEGF), a potent vasoactive cytokine, mediates the pathological angiogenesis and hyperpermeability associated with several chorioretinal vascular disorders including neovascular age-related macular degeneration (AMD). Attempts to stabilise and improve the condition of patients with AMD have led to the development and subsequent Food and Drug Administration (FDA) approval of two drugs with anti-VEGF action: pegaptanib[1] sodium (Macugen, a pegylated aptamer from Eyetech/OSI, New York, USA) and ranibizumab[2 3] (Lucentis), a recombinant, humanised, antibody fragment from Genentech Inc (San Francisco, California, USA). In addition, administration of intravitreal bevacizumab (Avastin), a full-length, recombinant, humanised antibody from Genentech and approved for the systemic treatment of metastatic colon cancer, appears to be useful for the treatment of neovascular AMD.[4] The intravitreal administration of each of these drugs is likely to achieve high intraocular concentrations with low systemic levels and few adverse effects.

VEGF Trap, a 110 kDa soluble protein, contains extracellular VEGF receptor sequences (VEGFR1 and VEGFR2) fused to an IgG backbone.[5] Although its intraocular duration of action is unknown, its high VEGF-binding affinity suggests a longer period of biological activity than ranibizumab.

This report presents a time-dependent mathematical model of intraocular VEGF Trap activity relative to ranibizumab.

METHODS AND RESULTS

VEGF Trap has a very high VEGF-binding affinity (K_d <1 pmol/l),[6] about [illegible] ranibizumab. On the basis of laboratory and clinical data, significant biological activity of ranibizumab (0.5 mg) persists for 30 days after intravitreal administration.[7]

If we assume that the intravitreal half-lives of antibodies and antibody fragments are proportional to their molecular masses, then we can predict the intravitreal half-life of VEGF Trap in primates even though it is not known. We know that its molecular mass is 110 kDa, approximately half way between that of ranibizumab (48 kDa) and that of bevacizumab (148 kDa). As a monkey model showed that rhuFab VEGF (a 48 kDa antibody fragment) has an intravitreal half-life of 3.2 days and rhuMab HER2 (a 148 kDa antibody similar to bevacizumab) has an intravitreal half-life of 5.6 days,[8] the half-life of VEGF Trap in a primate eye may be reasonably estimated as 4–5 days. In a rabbit model, VEGF Trap concentration decreased according to first-order kinetics, with a half-life of 4.79 days (unpublished data from Regeneron Pharmaceuticals, Tarrytown, New York, USA); this value was used for the calculations that follow.

A pharmacokinetic single-compartment rabbit model showed that intravitreal bevacizumab concentration decreases according to first-order decay.[9] Therefore, after a 1.15 mg injection of VEGF Trap (1.15 mg VEGF Trap is equimolar to 0.5 mg ranibizumab), the intravitreal biological activity of VEGF Trap, relative to ranibizumab, can be calculated according to the following equation:

$$A_t = A_r e^{-kt}$$

where A_t is the time-dependent VEGF activity, A_r is the baseline VEGF activity relative to ranibizumab, and k is a VEGF Trap time-dependent constant. Figure 1 shows this relationship graphically. VEGF Trap activity at 79 days equals that of ranibizumab at 30 days.

One treatment arm in the recently completed phase 2 VEGF Trap trial used a 4 mg dose. After a 4 mg VEGF Trap injection, the time-dependent intravitreal anti-VEGF activity, relative to 0.5 mg ranibizumab, can be calculated according to the following:

$$A_t = A_r C_r e^{-kt}$$

where C_r is the molar concentration of injected VEGF Trap relative to 0.5 mg ranibizumab. Figure 2 shows this relationship graphically. On day 87 after a 4 mg VEGF Trap injection, the relative biological activity would be comparable to ranibizumab at 30 days. Doses of 0.5 mg and 2 mg [illegible]

Mylan v. Regeneron, IPR2021-00880
U.S. Pat. 9,669,069, Exhibit 2011

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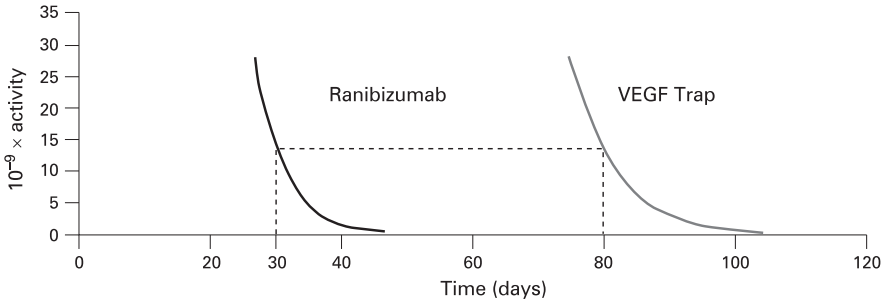

Figure 1 Time-dependent intravitreal activity of 1.15 mg VEGF Trap compared with that of 0.5 mg ranibizumab. The biological activity of VEGF Trap at 79 days is comparable to that of ranibizumab at 30 days.

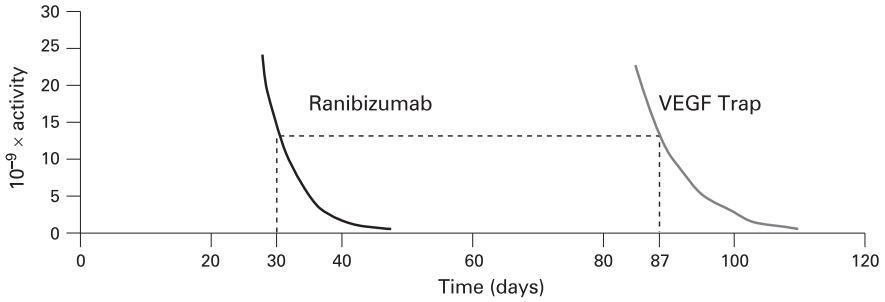

Figure 2 Time-dependent intravitreal activity of 4 mg VEGF Trap compared with that of 0.5 mg ranibizumab. The biological activity of VEGF Trap at 87 days is comparable to that of ranibizumab at 30 days.

DISCUSSION

At 10 weeks after an injection, the intraocular biological activity of VEGF Trap is theoretically comparable to the activity of ranibizumab at 30 days. This prolonged biological activity can be explained by the higher VEGF-binding affinity of VEGF Trap and its presumed longer intravitreal half-life when compared with ranibizumab. If this theoretical model is correct, then the advantages of VEGF Trap will include less frequent drug administration, resulting in fewer physician appointments and ancillary tests, lower overall cost, less cumulative risk from intravitreal injections, and the potential for improved patient compliance. However, it should be appreciated that, by increasing the intravitreal dose of VEGF Trap from 1.15 mg to 4 mg, there is only a marginal increase in the relative biological activity from 79 days to 87 days compared with ranibizumab at 30 days, and this increased dose may not be worth the increase in potential systemic adverse events. Consequently, there seems to be little advantage to increasing the dose above 1 mg unless a much higher initial dose results in greater suppression of VEGF and less frequent dosing overall because of the increased initial potency of the 4 mg dose.

A similar analysis comparing the biological activities of ranibizumab with bevacizumab showed that the two drugs were comparable after 27–38 days.[10] This can be explained by the lower affinity of bevacizumab for VEGF-A combined with longer half-life of bevacizumab compared with ranibizumab. In contrast with bevacizumab, VEGF Trap has both a longer intravitreal half-life because of its larger size and a much higher affinity for VEGF-A than ranibizumab, resulting in the greater theoretical duration of biological activity in the eye.

If our assumptions for the half-life and relative biological activity of VEGF Trap are correct, then the modelling presented in this paper supports less frequent dosing of VEGF Trap compared with ranibizumab for the treatment of neovascular AMD. This approach will be tested in the upcoming phase 3 trial with VEGF Trap.

Competing interests: None.

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