Received: 19 February 2020 | Revised: 15 July 2020 | Accepted: 11 September 2020

DOI: 10.1111/bcp.14776

COMMENTARY

Clinical ophtalmo-pharmacology. Looking ahead

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The eye plays an important role in pharmacology as it is one of the easiest places to observe the function of the autonomic nervous system in the reaction of the pupil. For a long time, the field was pharmacologically limited to eye drops that did affect the local autonomic system, and the autonomic nervous system was the area where (clinical) pharmacologists felt most comfortable.[1] Consequently, we largely considered the eye as a useful device to study autonomic effects.[2] The eye generally gets limited attention in the major pharmacology textbooks. Yet there have been momentous advances in drug treatment of ophtalmological diseases, and we felt this short commentary would be useful to correct this myopia.

Treatment of age-related degeneration of the macula is of course the most spectacular development in therapeutics recently after earlier and perhaps less spectacular advances in the treatment of glaucoma by beta blockers and prostaglandin analogs. Interestingly, the drug development for the intraocular administration of anti-vascular endothelial growth factor antibodies occurred around 2005 by Rosenfeld et al.[3] in an approach using a maximum tolerated intraocular dose. This was something we commented on in *BJCP* as not exactly the right approach[4] but too late. The possibility of injecting a medicine more or less where it was supposed to work may have lured the clinical pharmacological community away from the eye. The lack of what we like most-making concentration-time curves-may have made us look away. However, there are extremely interesting kinetic approaches, with admittedly some design creativity. We demonstrated clear peripheral concentrations of dexamethasone after peribulbar injection and managed to follow the intraocular pharmacokinetics with a population approach.[5–7] The same method was used to demonstrate that a potentially interesting anti-thrombin agent (for the treatment of contractile retinal detachment (PVR) reaches a therapeutic concentration in the eye.[8,9] So the clinical pharmacology and pharmacodynamics of medicines and medicine-device combinations need a revival, especially as ophthalmological medicines are in the group with the highest probability of approval after Phase I.[10] What can we expect to be commonly used in the next 5 years?

In most countries, the injection of anti-VEGFs is the most frequently performed intraocular procedure (in the Netherlands 400,000 in 2019), superseding the earlier champion of all surgical procedures performed: cataract surgery. Unfortunately, it also replaced cataract surgery as the first cause of postoperative endophthalmitis. Interestingly, it was in the treatment of postoperative endophthalmitis that direct intravitreal injection (of antibiotics) found its place in ophthalmology, with subsequent studies of intravitreal pharmacokinetics.[11,12] The focus of development is on longer acting anti-VEGF variants requiring less frequent injections (at this moment, the interval between injections is 4 to 8 weeks at best in what appears to be a life-long treatment) or targeting additional receptors for better effectivity. Biologicals are mainly used systemically for severe forms of uveitis but are also injected intravitreally to limit systemic side effects, as are the older anti-proliferative agents such as methotrexate. The evergreen steroids are also being administered in an intravitreal slow release form with a shorter action in practice than initially predicted (Ozurdex: not 6 months but 3 months) with, however, the same high risk of an increased intraocular pressure leading to glaucoma.[13] An even more targeted approach is the subretinal injection of drugs, initially to inject tissue plasminogen activator (TPA) to liquify submacular hemorrhages for displacement from the macula. In this approach, generally performed in combination with a vitrectomy, a small-bore needle (41 gauge) is used to perforate the retina and create a subretinal bleb.

This method will also be used in gene therapy for the delivery of gene carriers directly to the cells to be transfected, that surround this bleb (retinal pigment epithelial cells or retinal photoreceptors), an example of which is the first EMA approved gene therapy for a form of juvenile retinitis pigmentosa, voretigene neparvovec.[14]

In the past years, *BJCP* also joined this innovative drive. For instance, the repurposing of phenytoin for protection of the retina was suggested by Chiosi et al.[15] The idea to replace intraocular injections of VEGF inhibitors by eye drops containing the multikinase inhibitor regorafenib was attractive and led to a Phase I study[16] with the expected low systemic exposure. Unfortunately, a therapeutic exploratory study failed due to presumed lack of exposure in the

eye.[17] This study gives a reminder that this could have perhaps been prevented by a more clinical-pharmacological approach.[7] Nutrition is not a medicine but the trial methodology similar especially when it is attempted to accomplish improvement of a condition like macular degeneration. Such studies of course suffer from the problem that many different molecules are given at the same time and again would benefit from a more pharmacological mechanistic approach.[18]

Clinical pharmacologists have to play a more important role in the development of these treatments than they do at present. We therefore hope that the number of ophtalmo-pharmacological submissions to *BJCP* will reflect that vision.

COMPETING INTEREST

There are no competing interests to declare.

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