STEROID IMPLANTS

Methods for delivering steroids may have reduced side effects

By Roibeard O’hEineachain in London

Steroid implants currently under development show promise in the treatment of intraocular inflammation with an improved side-effect profile compared to implants currently in use, said Baruch D Kuppermann MD, PhD, University of California, Irvine, California, US at the 11th EURETINA Congress.

“The most important concept with these drug delivery systems is that very small amounts of drug can be used very effectively to treat disease for a prolonged period of time. So systemic exposure is limited, as well as the need for repeated injections,” Dr Kuppermann said.

The first intravitreal steroid implant to be marketed was the Retisert (Bausch + Lomb). The implant is sutured to the eye wall using a 3.5mm pars plana incision. It contains 0.5mg fluorocinolone acetonide, which it releases at a rate of approximately 3.0 to 5.0 micrograms per day and is designed to last up to three years.

In a preliminary clinical trial comparing the implant’s efficacy at four dosages, 0.59mg, 2.0mg, 3.0mg and 6.0mg, the lowest dosage, which was expected to have nearly no effect, turned out to be very effective, Dr Kuppermann said.

The FDA granted approval for the implant’s use in uveitis. However, they held back on approving the agent for diabetic macular oedema (DME) because, despite the low amount of drug it delivered, it had very significant side effects, chiefly cataract and intraocular pressure elevation.

He noted that nearly all the patients with the implant in the FDA trial developed cataracts. Although that might be acceptable for uveitis patients, the situation is more debatable in the case of patients with DME, he said. But of much greater concern was the implant’s effect on IOP, with 40 per cent of eyes needing filtration surgery to control the IOP, he pointed out.

“That became a concern, acceptable perhaps in uveitis patients, considering that the alternative is steroids or other toxic drugs, but for diabetics this was deemed not a fair trade-off in diabetic macular oedema, so the company decided to pass on the diabetic indication,” he added.

Implant easier on eye

However, there is now a smaller implant, The Iluvien (Alimera) also using fluorocinolone acetonide, which appears to have a less severe effect on IOP, Dr Kuppermann said. The implant is injected into the eye, rather than sutured into the eyeball, using a 25-gauge injector, he noted. It contains roughly half the amount of drug as the Retisert. There are two versions of the implant, one with a high dose of 0.5 micrograms per day that lasts for 18 months and the low dose 0.2 micrograms per day, which lasts for 24 to 36 months.

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A clinical trial involving patients with DME, the Fluocinolone for Macular Edema (FAME) study, showed that at both dosages of the Iluvien implant around a third of patients gained 15 or more letters, compared to only 17 per cent of patients receiving standard of care. Moreover, although 75 per cent of patients developed cataracts, only five per cent requires filtering surgery, compared to 40 per cent with the Retisert implant.

Another implant is the I-Vation from SurModics, a titanium-based helical coil designed for delivering triamcinolone acetonide, is screwed into the pars plana. However, this implant is something of an orphan because although in clinical trials it met most of its treatment goals, in terms of reduced retinal thickness and improved visual acuity, one patient with the implant developed retinal detachment and another developed endophthalmitis. In addition, about a third of patients needed to be on glaucoma drops and all developed cataracts.

“This drug delivery system is on hiatus right now looking for another home,” Dr Kuppermann said.

Meanwhile, Allergan has acquired a biodegradable dexamethasone implant, the Ozurdex, originally developed by Oculex. Unlike the Retisert and the Iluvien implants, it does not leave an empty husk behind once the drug is used up. Instead, as the drug is released, the implant’s polymer, polyactic glycolic acid, biodegrades to lactic acid glycolic acid, water and carbon dioxide.

“What attracted Allergan to purchase this company is that by varying the proportion of drug to polymer and the composition of the polymer it is possible to have a highly programmable drug delivery system so they are looking at brimonidine and other drugs as well in these polymer based systems,” Dr Kuppermann said.

In the PLACID trial, which compared laser alone to laser in combination with six monthly injections of Ozurdex, the implant performed significantly better than laser alone throughout 12 months of follow-up. In addition, only 15 per cent of eyes required IOP-lowering medication.

Another completely different approach under development by a French Company called Novagali, is to inject dexamethasone in a pro-drug form. The pro-drug’s chemical structure, dexamethasone palmitate, is relatively inert in the aqueous and the vitreous and is therefore less likely to affect the lens or the trabecular meshwork. However, in the retina it breaks down and becomes active. A Phase I, Open-Label, Dose-Escalation Clinical Study is under way.