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COMMENT

Ranibizumab port delivery system (RPDS): realising long awaited dream of prolonged VEGF suppression

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Ranibizumab (Genentech, South San Francisco, CA, USA) was a revolutionary anti-VEGF molecule approved by FDA in 2006 for neovascular age-related macular degeneration (nAMD). It had a paradigm-shifting effect on the treatment of various retinal neovascular pathologies, especially in nAMD and diabetic macular oedema (DME) [1, 2]. Ranibizumab monthly dose regimen has brought down the blindness attributable to nAMD by 72% and thus has provided a new lease of functional and quality life to the patients [2].

Since the introduction, except for a biosimilar that was approved for the Indian market, there has not been any advancement for the molecule per se [3]. The dosing, the delivery system, and the efficacy and safety have all been stagnant for the last 13 years [1]. In 2016 and 2018, the FDA had approved pre-filled syringes for ranibizumab in 0.5 mg dose and 0.3 mg dose, which was the first improvement in the delivery system since its launch [1]. Multiple trials have provided us with some guidelines such as monthly, pro re nata (PRN) and Treat and Extend (TREX). However, they all have a common denominator of being multiple injections regimen [4–6].

Ranibizumab port delivery system (RPDS) is an implantable, reservoir-based, slow-release platform. It sits in the sclera and delivers ranibizumab in a concentrated solution at different doses in the setting of nAMD. RPDS is a transforming pharmaceutical innovation to overcome the hurdle of frequent intravitreal injections [7]. Multiple, frequent injections over time carry a higher, cumulative risk of adverse events such as haemorrhage, inflammation, ocular hypertension, and infection, as well as an increased financial burden on the patients [8]. It also leads to poor patient compliance in long-term therapy and loss of the initial visual gains over time in many patients based on real-world utlization study outcomes. RPDS provides an opportunity to have an implant introduced into the vitreal cavity by a surgical procedure and refill of that implant as an office-based procedure. Recently Phase 2 results of the RPDS were revealed by Genentech and were termed the LADDER (Long Acting Delivery of Ranibizumab) trial [7]. This trial showed a promising outcome for the implant. The trial comprised of 4 arms being evaluated; namely RPDS 10 mg/ml, 40 mg/ml, 100 mg/ml, and monthly 0.5 mg injections. Two hundred and thirty two ranibizumab-responsive patients with nAMD were recruited in the study, and data from 220 patients was considered for analysis. The RPDS implant was filled with 0.02 ml of a customised formulation of ranibizumab in varying concentrations. This formulation is different from the FDA approved formulation used in the monthly injection regimen [9]. The refill time was determined by a set protocol that included subjective and objective end points. The results demonstrated that 100 mg/ml RPDS had a similar visual outcome to monthly ranibizumab injections. It had a mean refill time of 15 months, with 80% of the patients not requiring a refill per protocol for the first 6 months. There was no significant difference between the mean refill time of 40 mg/ml and 100 mg/ml arm but 100 mg/ml had a better visual outcome [7]. The promising results have led to the Phase 3 ARCH-WAY trial [10]. It is a multicenter, randomised, open-label study comparing safety, efficacy, and pharmacokinetics of 100 mg/ml solution for RPDS with 0.5 mg (10 mg/ml) solution of ranibizumab for intravitreal injections, and is expected to be completed by May 2022. In tandem,

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Genentech has also initiated the long-term efficacy and safety trial for the RPDS, which includes patients who successfully participated in the LADDER and ARCHWAY trials. Dubbed as PORTAL trial, it will evaluate 500 participants for 144 weeks with 24 weeks periodic refill of 100 mg/ml formulation for various outcomes. The trial is expected to be completed by June 2022 [11].

To realise the goal of long-term VEGF suppression, RPDS has gone through various stages and modification, such as laser photocoagulation of pars plana uvea at the scleral incision used to insert the device. It has significantly made the procedure safer by bringing down the rate of postoperative vitreous haemorrhage. The implantation procedure allows for the device to be secured in a well-tolerated, self-retaining, sutureless fashion, and the office-based refill approach performed on an infrequent basis makes it attractive for widespread clinical use in the future [7].

RPDS is poised to provide relief to patients who do not want to undergo frequent anti-VEGF injections. In addition, it may help to minimise the relative undertreatment that occurs in the real-world setting and better maintain vision gains over time in patients with nAMD [12]. Clinicians are looking forward to the results of the phase III ARCHWAY clinical trial. If this deliver system is successful in the treatment of patients with nAMD, it could also transform the other diseases with injection burden such as macular oedema related to diabetic retinopathy and retinal vein occlusion. RPDS is the first successful step towards attaining a truly long-acting anti-VEGF delivery. It will help pave the way for other strategies of long-term VEGF suppression such as injectable biodegradable polymer implants, drug encapsulation in injectable liposomes, microparticles and nanoparticles.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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