From Petunias to the Present- A Review of Oligonucleotide Therapy

Murali Krishna*
Surgical Specialist, Military Hospital, Palampur, India

*Corresponding author: Murali Krishna
murali276@yahoo.com
Surgical Specialist, Military Hospital, Palampur, India.
Tel: 91-8411066008


Abstract
Oligonucleotide therapy has come a long way since the early days. Ongoing research is finding more and more applications for this therapeutic tool. At present there are six FDA approved drugs based on oligonucleotide therapy. These are fomivirsen for treatment of CMV retinitis in AIDS patients, mipomersen for treatment of familial hypercholesterolemia, defibrotide for treatment of veno-occlusive disease in liver, eteplirsen for treatment of Duchene Muscular Dystrophy, pegaptanib for treatment of neovascular age related macular degeneration and nusinersen for management of spinal muscular atrophy.

Keywords: Oligonucleotide; Fomivirsen; Mipomersen; Defibrotide; Eteplirsen; Pegaptanib; Nusinersen

Introduction
RNA interference has come a long way since its initial discovery in 1990. What started out as a trial to get deeper colour for petunias by Napoli and Jorgensen [1] has now evolved into a cutting edge tool. The work done by Guo and Kemphus [2] and Fire and Mello [3] has paved way to this point. RNA interference also known as oligonucleotide therapy is currently being used in several fields ranging from pest control to management of genetic disorders. Currently, there are six FDA approved drugs based on oligonucleotide therapy and this review gives a short coverage of these six drugs.

Fomivirsen
Fomivirisen (ISIS 2922) is a oligonucleotide therapy targeting CMV IE gene expression. It was marketed for treatment of CMV retinitis in immune suppressed conditions like AIDS and was administered as an intravitreal injection [4]. FDA approved the drug for therapy in August 1998 and was the first anti-sense drug to be approved [5]. The drug has subsequently been withdrawn from market due to reduced incidence of CMV retinitis due to better therapy of AIDS using HAART [6].

Mipomersen
Mipomersen was approved by FDA in January 2013 [7-9]. It is an antisense oligonucleotide inhibitor of apoB, used as an adjunctive therapy to lower LDL-c, apoB, TC and non HDL-C levels in patients of Familial Hypercholesterolemia. It causes the activation of RNase-H which catalyzes RNA cleavage and prevents protein translation thus causing reduced level of apoB. Phase 3 clinical trials clearly showed the efficacy of Mipomersen in patients of Homozygous familial Hypercholesterolemia. Raal et al. [10] reported a -24.7% change in LDL-C level as compared to -3.3% change with placebo. McGowan et al. [11] reported -35.9% change in LDL-C levels when compared to 12.5% in placebo. This therapy was in addition to other standard lipid lowering medication at maximum permissible dosage and lifestyle changes as per NCEP-ATP III guidelines [12].

The suggested dose of Mipomersen is 200 mg subcutaneous once weekly [13]. The adverse event most commonly reported was injection site reaction. Other serious adverse events include hepatotoxicity, renal adverse events and cardiac events like Myocardial infarction, angina and CAD [11]. Due to the predominance of hepatic side effects, baseline AST, ALT, ALP and serum bilirubin are supposed to be noted before start of therapy. Also periodic monitoring of ALT and AST levels are to be done. More than three times elevation of AST or ALT levels calls for withholding the dose and identifying the likely cause for elevation.

Defibrotide
Defibrotide is a mixture of single stranded and double stranded oligonucleotides derived from porcine intestinal mucosa. It has shown to have anti atherosclerotic, anti ischemic and anti thrombotic properties [14-16]. It has been suggested for therapy...
of veno-occlusive disease (VOD) occurring in liver after high dose chemotherapy and stem cell transplantation.

The mechanism of action of the drug is exactly not known but the main target of the drug is endothelium [15]. Defibrotide causes its effects by a multi-pronged action on several aspects of endothelial physiology. It causes an increase of prostacyclin and prostaglandin E2 and decrease in concentration of leukotriene B4 [17]. It also causes activation of fibrinolytic system by increasing tissue plasminogen activation [18,19]. Other effects include reduced thrombin generation, reduced tissue factor expression and endothelin activity [20]. The drug also negates the proapoptotic effect of chemotherapy on endothelium [21].

The role of defibrotide in VOD was elucidated by Richardson and colleagues in 1998. The study showed a complete response in 22 out of 40 patients [22]. Several studies subsequently conducted has reported a complete response rate of more than 50% and increased survival benefit. Various studies used differing doses of the drug varying from 5 mg/kg to 120 mg/kg and the route of drug administration was intravenous or oral [23-30]. No significant side effects have been reported for the drug even at high doses. Newer application of the drug in treatment of malignancy and multiple myeloma are under research.

**Eteplirsen**

Eteplirsen was developed by Sarepta therapeutics and was approved by FDA in September 2016 [31]. It was granted an accelerated approval as it increased the level of dystrophin in patients of Duchene Muscular Dystrophy [31,32] and a complete approval is pending for results of additional clinical trials.

The mechanism of action of the drug is called exon skipping. It causes a change in translational reading frame of a gene thus altering the final product [33,34]. Eteplirsen binds to exon 51 of DMD gene [35] and causes skipping of this particular exon while splicing [33]. This results in a functional albeit shortened dystrophic protein. This drug targets DMD mutation with deletion ending at exon 50 and starting at exon 52 [36] which comprises of 14% of all DMD patients [37].

The recommended dose is 30 mg/kg/week given as an IV infusion. The decision of approval by FDA was based on four studies- NC T00844597, NC T01396239/ NC T01540409 [38-40] and NC T02255552 [32]. Though the studies showed a positive increase in the level of dystrophin they are plagued with several concerns like absence of good control, low sample size, short heterogeneity, reproducibility and reliability [38]. The drug is generally well tolerated with no serious adverse effects noted in any trials. Further modification of drug to enhance its uptake and efficacy will benefit a larger portion of affected patients.

**Pegaptanib**

Pegaptanib sodium was approved by FDA in December 2004 for management of neovascular age related macular degeneration (ARMD). It acts by binding to VEGF and preventing activation of VEGF receptors in eye and thereby stopping angiogenesis [41].

The FDA approval comes following a phase III study evaluating the efficacy of Pegaptanib. This study, known by the acronym VISION, administered total of 7545 intravitreous injection of pegaptanib and 2557 sham injections. The difference in patients was visible from the first follow up visit at 6 weeks. On further follow up, patients receiving placebo was twice likely to develop severe vision loss [42].

The recommended dosage is 0.3 mg intravitreous injection administered once every 6 weeks [43]. The solution must be inspected for presence of any floaters or change in colour and strict aseptic technique should be followed. The injection is supplied in single use 1 mL syringe containing 0.3 mg pegaptanib in 90 microlitre volume. It should be stored in refrigerator at 2°C-8°C. The adverse effects reported in VISION study included vitreous floaters, vitreous opacities and anterior chamber inflammation which was significant when compared to sham group. Other non significant adverse effects include eye pain, punctuate keratitis and corneal edema. Injection related adverse effects include endophthalmitis, retinal detachment and traumatic injury to lens [42].

**Nusinersen**

Nusinersen is an antisense oligonucleotide modulating splicing of SMN2 pre mRNA and increase production of full length SMN protein [44]. The decreased level of SMN protein is responsible for Spinal Muscular Atrophy, a rare and crippling autosomal recessive disorder [45]. The drug was approved by FDA in December 2016.

Phase II studies showed promising safety and efficacy and demonstrated an increase in full length SMN2 mRNA and SMN protein levels. Most of the treated infants achieved new milestones [46]. Phase III study was a double blind sham-procedure controlled study. The inclusion criteria was genetic diagnosis of SMA with 02 copies of SMN2 gene, onset of symptoms at age less than 06 months and age less than 07 months with no hypoxemia on screening. The study demonstrated a statistically significant percentage of motor milestone responders during the interim efficacy analysis [47].

The drug is administered by intrathecal injection and dosing regimen is 12 mg every 14 days for 3 doses and then a fourth loading dose of 12 mg intrathecaly 30 days after the loading dose. No serious adverse effects were reported during the study [47].

**Conclusion**

Oligonucleotide therapy has provided solutions to diseases which were earlier considered untreatable. However, the steep cost of the drug has prevented this treatment from being available for the masses. Further innovations in RNA interference technology may help in finding better and affordable cure to many more diseases.
References


4. Randomized dose-Comparison studies of intravitreous fomivirsen for treatment of cytomegalovirus retinitis that has reactivated or is persistently active despite other therapies in patients with AIDS. Am J Ophthalmol 2002: 475-473.


8. FDA News Release: FDA approves new orphan drug Kynamro to treat inherited cholesterol disorder.


32. US Food Drug Administration (2016) Application number 206488Srig1s000: summary review.


35. http://www.dmd.nl/