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From Petunias to the Present- A Review of Oligonucleotide Therapy

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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

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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 The drug has subsequently been withdrawn from market due to reduced incidence of CMV retinitis due to better therapy of AIDS using HAART [6].

Mipomeresen

Mipomeresen 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 Hypercholestrolemia. 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 Hypercholestrolemia. Raal et al. [10] reported a -24.7% change in LDL-C level as compared to -3.3% change with placebo. Mc Gowan 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 Mipomeresen 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 leukotreine B4 [17]. It also causes activation of fibrnolytic system by increasing tissue plasminogen actrivation [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, chort 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

Peagaptanib 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 storedin 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 intrathecally 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

1 Napoli C, Lemieux C, Jorgensen R (1990) Introduction of a chimeric chalcone synthase gene into petunia results in reversible co-suppression of homologous genes in trans. Plant Cell 2: 279-289.

2 Guo S, Kemphues KJ (1995) par-1, a gene required for establishing polarity in C. elegans embryos, encodes a putative Ser/Thr kinase that is asymmetrically distributed. Cell 81: 611- 620.

3 Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, et al. (1998) Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature 391: 806-811.

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.

5 Roush W (1997) Biotechnology: Antisense Aims for a Renaissance. Science 276: 1192-1193.

6 http://www.isispharm.com/Pipeline/Therapeutic-Areas/Other.htm

7 www.kynamro.com/~/media/Kynamro/Files/kynamro-pi.pdf

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

9 https://www.fda.gov/default.htm

10 Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, et al. (2010) Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia: A randomised, double-blind, placebocontrolled trial. Lancet 375: 998-1006.

11 McGowan MP, Tardif JC, Ceska R, Burgess LJ, Soran H, et al. (2012) Randomized, Placebo-Controlled Trial of Mipomersen in Patients with Severe Hypercholesterolemia Receiving Maximally Tolerated Lipid-Lowering Therapy. PLoS ONE 7: e49006-e49006.

12 Grundy S, Becker D, Clark LT, Cooper RS, Denke MA, et al. (2002) Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Circulation-Hagertown 106: 3143-3421.

13 Kynamro (mipomersen sodium) injection solution for subcutaneous injection, prescribing information. Cambridge, Mass.: Genzyme Corp.

14 Coccheri S, Biagi G (1991) Defibrotide. Cardiovasc Drug Rev 9: 172-196.

15 Palmer KJ, Goa KL (1993) Defibrotide. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in vascular disorders. Drugs 45: 259-294.

16 Falanga A, Vignoli A, Marchetti M, Barbui T (2003) Defibrotide reduces procoagulant activity and increases fibrinolytic properties of endothelial cells. Leukemia 17: 1636-1642.

17 Coccheri S, Biagi G, Legnani C, Grauso F (1988) Acute effects of defibrotide, an experimental antithrombotic agent, on fibrinolysis and blood prostanoids in man. Eur J Clin Pharmacol 35: 151-156.

18 Berti F, Rossoni G, Biasi G, Buschi A, Mandelli V, et al. (1990) Defibrotide, by enhancing prostacyclin generation, prevents endothelin-1 induced contraction in human saphenous veins. Prostaglandins 40: 337-350.

19 Zhou Q, Chu X, Ruan C (1994) Defibrotide stimulates expression of thrombomodulin in human endothelial cells. Thromb Haemost 71: 507-510.

20 Sato Y, Asada Y, Hara S, Marutsuka K, Tamura K, et al. (1999) Hepatic stellate cells (Ito cells) in veno-occlusive disease of the liver after allogeneic bone marrow transplantation. Histopathology 34: 66-70.

21 Eissner G, Multhoff G, Gerbitz A, Kirchner S, Bauer S, et al. (2002) Fludarabine induces apoptosis, activation, and allogenicity in human endothelial and epithelial cells: protective effect of defibrotide. Blood 100: 334-340.

22 Richardson PG, Elias AD, Krishnan A, Wheeler C, Nath R, et al. (1998) Treatment of severe veno-occlusive disease with defibrotide: compassionate use results in response without significant toxicity in a high-risk population. Blood 92: 737-744.

23 Chopra R, Eaton JD, Grassi A, Potter M, Shaw B, et al. (2000) Defibrotide for the treatment of hepatic veno-occlusive disease: results of the European compassionate-use study. Br J Haematol 111: 1122-1229.

24 Richardson PG, Murakami C, Jin Z, Warren D, Momtaz P, et al. (2002) Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. Blood 100: 4337-4343.

25 Richardson PG, Soiffer RJ, Antin JH, Voss SD, Jin Z, et al. (2004) Defibrotide (Df) for the treatment of severe veno-occlusive disease (VOD) and multi-organ failure (MOF) post SCT: final results of a phase II, multicenter, randomized study and preliminary analyses of surrogate markers and ultrasound findings. Blood 104: 350.

26 Ramasamy K, Lim ZY, Pagliuca A, Grundy R, Devereux S, et al. (2006) Incidence and management of hepatic veno-occlusive disease in 237 patients undergoing reduced-intensity conditioning (RIC) haematopoietic stem cell transplantation (HSCT). Bone Marrow Transplant 38: 823-824.

27 Corbacioglu S, Greil J, Peters C, Wulffraat N, Laws HJ, et al. (2004) Defibrotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multicentre study demonstrates therapeutic efficacy upon early intervention. Bone Marrow Transplant 33: 189-195.

28 Bulley SR, Strahm B, Doyle J, Dupuis LL (2007) Defibrotide for the treatment of hepatic venoocclusive disease in children. Pediatr Blood Cancer 48: 700-704.

29 Haussmann U, Fischer J, Eber S, Scherer F, Seger R, et al. (2006) Hepatic veno-occlusive disease in pediatric stem cell transplantation: impact of pre-emptive antithrombin III replacement and combined antithrombin III/defibrotide therapy. Haematologica 91: 795-800.

30 Carreras E, Olavarria E, Neven B, Maertens J, Boelens JJ, et al. (2007) Defibrotide for the treatment of veno-occlusive disease post SCT: preliminary results of EU compassionate use program in 332 patients confirm promising activity and manageable toxicity. Blood 110: 613.

31 Food Drug Administration (2016) FDA grants accelerated approval to first drug for Duchenne muscular dystrophy Silver Spring. US FDA.

32 US Food Drug Administration (2016) Application number 206488Orig1s000: summary review.

33 Kole R, Krieg AM (2015) Exon skipping therapy for Duchenne muscular dystrophy. Adv Drug Deliv Rev 87: 104-107.

34 Lee JJA, Yokota T (2013) Antisense therapy in neurology. J Pers Med 3: 144-176.

35 http://www.dmd.nl/

36 van Deutekom JC, van Ommen GJ (2003) Advances in Duchenne muscular dystrophy gene therapy. Nat Rev Genet 4: 774-783.

37 Bladen CL, Salgado D, Monges S (2015) The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. Hum Mutat 36: 395-402.

38 Cirak S, Arechavala GV, Guglieri M (2011) Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet 378: 595-605.

39 Mendell JR, Rodino KLR, Sahenk Z (2013) Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol 74: 637-647.

40 Mendell JR, Goemans N, Lowes LP (2016) Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol 79: 257-271.

41 Vinores SA (2003) Technology evaluation: Pegaptanib, Eyetech/ Pfizer. Curr Opin Mol Tker 5: 673-679...

42 Gragoudas ES, Adamis AP, Cunningham ET (2004) For the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular agerelated macular degeneration. N EnglJ Med 351: 2805-2816.

43 Macugen (2004) NewYork: Eyetech Pharmaceuticals, Inc, and Pfizer Inc.

44 Hua Y, Sahashi K, Hung G, Rigo F, Passini MA, et al. (2010) Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. Genes & Development 24: 1634-1644.

45 Prior TW (2010) Spinal muscular atrophy: a time for screening. Curr Opin Pediatr 22: 696-702.

46 Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, et al. (2016) Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 388: 3017-3026.

47 Finkel R, Kuntz N, Mercuri E, Chiriboga C, Darras B, et al. (2017) Efficacy and safety of nusinersen in infants with spinal muscular atrophy (SMA): Final results from the phase 3 ENDEAR study. European Journal of Paediatric Neurology P: 21.