

Medicinal Applications of Antisense Oligonucleotides: A Review

Kavya Pandiri^{1*}, Mohammed Abdul Samad¹, Nadeem Abbas Gulamus², Hajera Khanam³

¹Department of Pharmacology, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad-500028, Telangana, India

²Department of Medicine, Foster Development Homoeopathic Medical College and Hospital, Aurangabad-431003, Maharashtra, India

³Department of Pharmacology, Shadan Women's College of Pharmacy, Khairatabad, Hyderabad-500004, Telangana, India

ABSTRACT

Antisense technology has emerged as a fast and conceivably high-throughput method for repressing genes due to advancement in knowledge about DNA and RNA physiology. The limitations of antisense oligonucleotide therapy in delivery strategies have been overcome in recent years. Antisense oligonucleotide treatment was effectively applied towards targeting a wide range of therapeutic areas. With ongoing approvals of antisense oligonucleotides, there is an expanding enthusiasm for increasing the utilization of these compounds for curing various infections. This short survey gives a far-reaching comprehension of applications of antisense technology, how they can be utilized therapeutically, and current endeavors to grow new antisense oligonucleotide treatments that will add a forthcoming therapeutic approach for the treatment of various diseases.

Keywords: Antisense, Cancer, COVID-19, Vaccine.

1. INTRODUCTION

In recent times, antisense technology has been developing as a fast and conceivably high-throughput molecular approach of treatment due to advancement in knowledge about DNA and RNA physiology. The fundamental idea is that when an oligonucleotide (a short, single-stranded RNA or DNA molecule complementary to an mRNA) is brought into a cell, it will explicitly tie to its complementary mRNA and stops protein synthesis. This happens in light of the fact that the mRNA no longer approaches the ribosome and the RNA is quickly debased by ribonuclease H. Consequently, the presentation of short DNA integral to mRNA will prompt a particular reduction or blockage of protein blend by a specific gene which results in turning off that gene, as shown in Figure 1.^{1,2}

There have been many issues related to the utilization of antisense technology. In numerous applications, these obstacles have been survived. Oligonucleotides can be blended with lipids causing easy absorption by cell membranes. Different procedures have likewise been created to encourage the take-up of oligonucleotides by

cells. Synthetic adjustment of the antisense oligonucleotides can render them progressively stable in cells and blood by expanding their protection from ribonuclease digestion.³

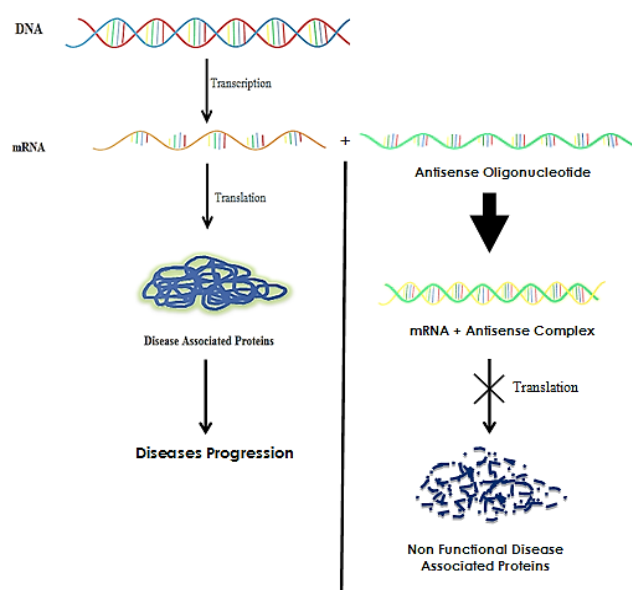


Figure 1: Mechanism of action of antisense oligonucleotide

Corresponding author

Kavya Pandiri

Email : kavyapandiri95@gmail.com

Received: 22-02-2020

Accepted: 15-03-2020

Available Online: 01-04-2020

2. EXTENDING NEW TECHNOLOGIES FOR TARGET SELECTION

A scope of *in vitro* techniques and procedures have been utilized to encourage the way towards the selection of target sites for antisense activity for checking the availability of target structures by RNase H mapping. Software exertions through computational endeavors are utilized to foresee the secondary structure and pattern of mRNAs which revealed excellent outcomes. While this attempt disregards other parameters (three-dimensional structure of RNA *in vivo* or the convenience of the target site for RNase H) that impact antisense efficacy, it may ominously decrease the number of Antisense Oligonucleotides (ASOs) required for screening. The expectation of target sites established on motif may additionally aid in the design of antisense therapeutics.⁴

3. APPLICATIONS

These are many potential uses of antisense oligonucleotides as shown in Figure 2. With increased advancement in chemistry, there are progressively viable oligonucleotides and quality vectors developed which have the capacity to meddle freely with the interpretation of explicit mRNAs.

Few of the approved antisense oligonucleotide drugs have been presented in Table 1.

3.1. Viral Diseases

3.1.1. SARS-CoV-2 (COVID-19)

The principal antisense action intended to inhibit translation of the viral replicase polyprotein was to reduce the luciferase expression in cell-free and transfected cell culture assays. Modified ASOs were screened for antiviral activity against a member of Coronaviridae,

mouse hepatitis virus (MHV). Morpholino oligomers with peptide conjugation repressed virus titers 10 to 100 fold in a sequence-specific and dose-responsive manner. These outcomes recommend the use of ASO for control of coronavirus infection.⁵

An urgent requirement for proficient medical treatments and vaccines epitomizes the harshness of the high transmission rated global COVID-19 pandemic, 2.6 to 4.7% lethality and a tremendous social and economic effect. As of now, there are just vague medicines to help the patients in intense respiratory trouble the chance of focusing on the SARS-CoV-2 genome by RNA treatment ought to be profoundly investigated. Barrey *et. al.*, 2020 developed two ASO designs focusing on transcripts

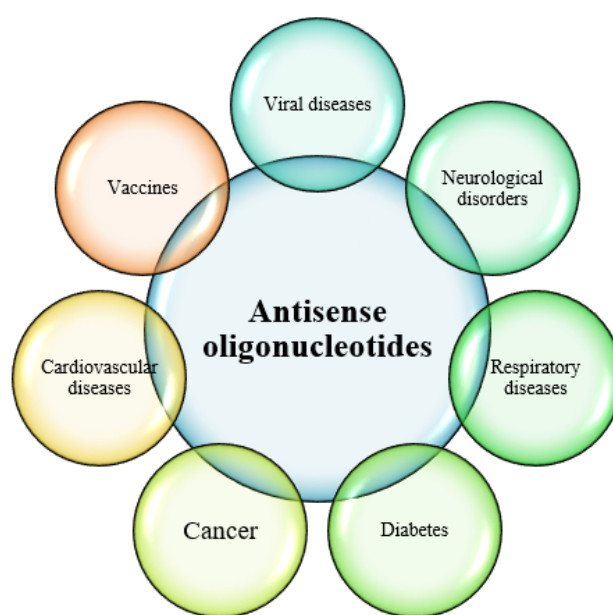


Figure 2: Applications of antisense oligonucleotides

Table 1: Approved antisense oligonucleotide drugs

Drug	Target	Disease
Eteplirsen	Exon 51	Duchenne muscular dystrophy
Mipomersen	apo B-100	Homozygous familial hypercholesterolemia
Patisiran	Mutant transthyretin	Polyneuropathy caused by hereditary transthyretin-mediated amyloidosis
Fomivirsen (withdrawn)	Immediate early region 2 (IE2) of human CMV	Cytomegalovirus retinitis
Inotersen	Wild-type TTR mRNA	Polyneuropathy caused by hereditary transthyretin-mediated amyloidosis
Nusinersen	Exon 7	Spinal muscular atrophy (SMA)
Trioxsalen	Interstrand cross-links in DNA	Antipsoriatic and vitiligo
Macugen	VEGF165	Age-related macular degeneration
Defibrotide	FGF2	Hepatic veno-occlusive disease
Givosiran	ALAS1 mRNA	Acute intermittent porphyria
Golodirsen	Dystrophin	Duchenne muscular dystrophy
Heplisav-B (Vaccine)	Induces specific humoral antibodies	Hepatitis B

ALAS1: 5-aminolevulinic acid synthase; CMV: Cytomegalovirus; TTR mRNA: Transthyretin messenger RNA; VEGF 165: Vascular endothelial growth factor 165; FGF2: Fibroblast growth factor 2

encoding viral proteins associated with replication and transcription of SARS-CoV-2, with an aim to block infection.

One ASO is conventional with modification in phosphorothioate and the other is a locked nucleic acid, i.e., GapmeR. ASOs target the genomic sequence at 5' untranslated region (5'-UTR), open reading frames 1a and 1b directing expression of the replicase or transcriptase complex, and the nucleoprotein gene N. The hetero-duplexes antisense oligonucleotide-RNA is cleaved by RNase H1, after binding the viral RNA target. The most potent GapmeR agent targets a key genomic domain, the 5'-UTR with numerous purposes in the viral cycle. These *in silico* results recommended encouraging advancement in translational exploration to combat the global COVID-19 pandemic.⁶

3.1.2. Ebola Virus Disease

There is no Food and Drug Administration (FDA) approved therapeutics against the fatal Ebola virus illness. ASO with locked nucleic acid was formulated for destroying the host factor Niemann-Pick C1, required for the Ebola virus to get into the cytoplasm of the host. Results from human and murine cell lines revealed 50% inhibitory concentration (IC₅₀) and 94% knockdown effectiveness which showed efficient NPC1 protein knockdown *in vitro* activity. Treatment with ASOs against the Ebola virus resulted in substantial reduction in virus titer, representing ASOs as a hopeful therapeutic approach for the curing infection.⁷

3.1.3. Hepatitis B

A locked nucleic acid single-stranded ASO was designed to attain a specific target on liver asialoglycoprotein receptor and reduces kidney contact. It was conjugated with three N-acetylgalactosamine moieties which direct specific binding on the superficial surface of hepatocytes. The results from animal studies revealed that N-acetylgalactosamine-conjugated locked nucleic acid single-stranded ASO have a strikingly higher level of potency when compared to its non-conjugated counterpart.⁸

3.1.4. Influenza Virus

Up to 20% of the population experience respiratory infections due to the influenza virus according to the WHO report. The highest antiviral activity was shown by the formulated morpholino analog and phosphoryl guanidine oligodeoxyribonucleotide (PGO) with the sequence of oligonucleotide PB1-2AUG-R targeted towards the AUG codon region of segment 2 of the virus genome. The influenza virus titer in MDCK cell culture was reduced by 40 times when PGO was used in the concentration of 20 μ M.⁹

3.1.5. Respiratory Syncytial Virus (RSV)

Severe RSV infections in infants cause bronchiolitis and cough that increases the possibility of developing asthma and death. Administration of IL-4R α specific ASO intranasally during primary infection to neonatal mice previously infected with RSV at 1-week and was again infected at 6 weeks of age showed less RSV infection and abolished the pulmonary dysfunction, which was inter-related with reduced Th2 responses, i.e., reduced goblet cell hyperplasia, Th2 cells, and cytokine secretion and enhanced Th1 responses, i.e., elevated Th1 cell numbers and type I Abs and cytokines.¹⁰

3.1.6. HIV AIDS

Combination antiretroviral therapy (cART) is an efficient therapeutic attempt for HIV-1 infection. Yet cART is associated with certain limitations which leads to the development and design of a modified ASO, i.e., 2'-deoxy-2'-fluoroarabinonucleotide (FANA) that targets highly protected zones in the HIV-1 genome. Results showed strong suppression of HIV-1 replication in HIV-1-infected human primary cells. *In vitro* mechanistic studies revealed that the activation of RNase H1 and steric hindrance of dimerization is liable for the inhibitory activity of FANA ASOs. The outcomes strongly recommended that FANA ASOs has abundant potential for antiretroviral therapy.¹¹

3.2. Neurological Disorders

3.2.1. Batten Disease

An investigational clinical protocol report was published in 2009 by the FDA revealing the development of ASO drug, milasen for Batten disease. Milasen was modified for a single patient's definite mutation and remains an investigational drug as it is not suitable for the treatment of other patients with Batten's disease. Though, it is an example of genomic medicine intervention.¹²

3.2.2. Neuropathic Pain

It is uncertain that which isoform of p38 impact the development of chronic pain. In a previous study, the effects of potent, p38 MAPK subtype-specific ASOs were screened in many chronic pain models after a single intrathecal injection (300 μ g/10 μ L) in CD1 mice. In the chronic constriction injury study model, p38 α MAPK ASO was administered on postoperative day 5, which was reported to decrease CCI-induced mechanical allodynia in male after the fracturing of the tibia but not in female mice with partial reduction (\approx 50%) of spinal p38 α or p38 β mRNA level in both the sexes. Pre-treatment with intrathecal p38 α MAPK ASO also prevented TLR4-mediated mechanical allodynia indicating that ASOs could be a novel treatment for certain chronic pain conditions.¹³

3.2.3. Spinocerebellar Ataxia-1

Spinocerebellar ataxia type 1 (SCA1) is caused by extension of a translated CAG recurrent encoding a glutamine tract in the ataxin-1 (ATXN1) protein. Up to now, there are no treatments available to modify its progressive fatal course. The therapeutic capability of an ASO targeting mouse *Atxn1* in *Atxn1154Q/2Q*-knockin mice was investigated. At 5 weeks of age, a single ASO treatment made mice free of these disease-associated phenotypes. Results findings indicated that the therapeutic significance of exactly targeting ATXN1 RNA expression with ASOs is an important attempt for treating lethality in SCA1.¹⁴

3.2.4. Duchenne Muscular Dystrophy

This is triggered by loss-of-function mutations in the dystrophin gene encoding for dystrophin. It is an X-linked recessive fatal neuromuscular disorder described by advanced degeneration of muscle and cardiomyopathy which affects newborn worldwide. Exon skipping using ASO is one of the most potential approaches, which effectively restored dystrophin expression in skeletal muscles and improved skeletal muscle function.¹⁵

3.2.5. Huntington's Disease (HD)

Huntington's disease is a prevailing neurodegenerative disorder that occurs due to extended CAG repeat in the huntingtin (HTT) gene, which impacts a toxic gain of function because of an extended polyglutamine tract in the resulting protein. ASOs intended to bring down HTT and has been appeared to give drawn-out progress in HD and the current drug is in the clinical trial phase.^{16,17}

3.2.6. Amyotrophic Lateral Sclerosis (ALS)

Though mutation in many genes leads to ALS, many studies reported ATXN2 as a therapeutic target for ALS. Almost more than 10% of ALS cases are due to mutations in superoxide dismutase 1 (SOD1) which alter its function. Phase-I clinical trials of human SOD1 ASO proved well tolerance of the drug when infused into the CSF. IONIS-SOD1Rx (BIIB067) is currently undergoing phase 3 clinical trials with the aim to target C9ORF72 for ALS GGGGCC repeat expansions in the C9ORF72 gene are causative of ALS and frontotemporal dementia.¹⁸

3.2.7. Alzheimer Disease (AD)

Reducing the whole tau protein by ASOs is associated with significant therapeutic methods pertinent for tauopathies (corticobasal degeneration, argyrophilic grain disease, progressive supranuclear palsy, and frontotemporal dementia). Ionis Pharmaceuticals Inc. is presently accomplishing a phase I/II study to evaluate the safety and tolerability of 2'MOE ASO in patients with mild AD. This ASO targets MAPT mRNA to reduce the quantity of tau protein regardless of its isoform.¹⁹

3.2.8. Parkinson's Disease (PD)

ASOs reducing LRRK2 in mice treated with α -synuclein (aSyn) preformed fibrils were associated with reduced aggregations of phospho(S129)- α -synuclein. Decreased aSyn concentrations result in preclusion and exclusion of aSyn pathology and avoid dysfunction of the dopaminergic cell. The results demonstrated the distribution of SNCA ASOs all through the brain of non-human primates and reduction in the levels of aSyn cerebral spinal fluid. The obtained data suggested the progress of SNCA ASOs as a possible disease altering therapy for PD and related synucleinopathies.²⁰

3.2.9. Spinal Muscular Atrophy (SMA)

SMA is caused by loss-of-function mutations in the SMN1 gene which results in the loss of the survival motor neuron (SMN) protein. The nusinersen, an ASO drug impedes an intronic splicing silencer element in the SMN2 intron 7 and avert the spliceosome from excluding exon 7. Nusinersen was approved by the FDA and well-tolerated in patients with SMA1.²¹

3.2.10. Multiple Sclerosis (MS)

More than 100 ASOs were formulated to prompt avoiding of individual exons of the integrin subunit alpha 4 (ITGA4) transcripts and thus, decreasing expression of the protein. Modified ASOs targeting ITGA4 were screened in the experimental autoimmune encephalomyelitis mouse model for their impact in deferring MS progression. The results showed that the developed ASO was highly specific to inhibit expression of the protein by way of interfering with normal exon and are relevant to various gene targets that endure splicing throughout the expression.²²

3.3. Cardiovascular Diseases

3.3.1. Thromboembolism

The clinical trial of ASO, volanesorsen was developed to reduce apoCIII mRNA levels and the drug presently is investigated in phase III clinical trials for the treatment of hypertriglyceridemias. The antisense drug IONIS-FXIRx was reported to lower the factor XI levels and can be effective than conventional antithrombotics. IONIS-FXIRx/BAY 2306001 phase II study is enduring to explore the effect of the drug in patients with end-stage renal disease on hemodialysis.^{23,24}

3.3.2. Familial Hypercholesterolemia

Mipomersen was approved by the FDA in 2013 that inhibits the action of the apolipoprotein B gene, employed in the treatment of homozygous familial hypercholesterolemia. It binds and degrades the low-density lipoprotein, very low-density lipoprotein, and apolipoprotein B-100

coded mRNA. Every individual prescribed for mipomersen was registered in a risk evaluation and mitigation strategies (REMS) program approved by the FDA.²⁵

3.3.3. *Thalassemia*

Beta-thalassemia is the most widely recognized hereditary disorder characterized by a decrease in beta-globin and ineffective erythropoiesis. Mouse and human genetic information from multiple groups suggested that decreasing the expression of TMPRSS6 can up-regulate hepcidin and recover the disease symptoms related with β -thalassemia. Potent ASOs against mouse TMPRSS6 resulted in hepcidin up-regulation and reduction in serum iron and transferrin saturation. In the mouse model of beta-thalassemia, TMPRSS6 reduction resulted in the induction of hepcidin and dramatic reductions of serum transferrin saturation with reduced liver iron concentration. Interestingly, lead ASO compounds were tested in normal monkeys revealed decreased TMPRSS6 mRNA levels, which collectively established that TMPRSS6 ASO is an effective therapeutic in beta-thalassemia and associated disorders.²⁶

3.4. Respiratory Diseases

Inhaled ASOs are emerging therapeutics for treating many respiratory diseases, such as, asthma and Chronic Obstructive Pulmonary Disorder (COPD). ASO therapy is a promising approach due to the direct target to the lung, avoiding systemic degradation, and minimizing adverse effects. Oligonucleotide therapies have been evaluated as potential therapeutics for treating asthma and other respiratory illness. The protein knockdown mechanism gives potentially more non-specific biological outcomes. EPI-2010 was used against the adenosine A1 receptor, which decreases hypersensitivity and inflammation in the lungs. Many ASOs are in clinical trials to measure the stability and potency of oligonucleotides in respiratory diseases.^{27,28}

3.4.1. *Cancer*

The ASOs can easily recognize mRNA and differentiate the normal and mutated oncogenes in tumor cells, which is a special advantage. Several studies have shown that ASOs can inhibit gene expression and thus, can be used to decrease the growth of tumors through affecting the cellular functions and protein synthesis. ASO therapy prevents abnormal expression and mutations in tumor cells. A chimeric 2'MOE modified antisense drug, i.e., custirsen targets the clusterin, is currently in phase III clinical trials for the treatment of prostate cancers. Danvatirsen, another ASO is in the investigation to target signal transducer and activates transcription 3 (STAT3) in various kinds of cancers. Many modified ASOs targeting

tumor cells are in the clinical trial as a possible treatment for cancer.²⁹

3.5. Diabetes

Since the past, laser photocoagulation and vitrectomy surgery are employed in the treatment of diabetic retinopathy. Second-generation ASOs are utilized in curing diabetic retinopathy which down-regulates the signal pathways of multiple growth factors that are associated with ocular angiogenesis and vascular leakage.³⁰

3.6. Inflammation and Autoimmune Diseases

ASO drugs are also assessed for many inflammatory diseases. Mongersen presented the hopeful effects on patients with ulcerative colitis targeting to the SMAD7 mRNA. Alicaforfen drug targeting intercellular adhesion molecule 1 (CD54) has been tested by systemic delivery for its effect in patients with pouchitis, inflammatory bowel disease, and ulcerative colitis. This drug is presently being developed for the treatment of Crohn's disease.^{31,32}

3.7. Hereditary Transthyretin-Mediated Amyloidosis

Inotersen (Tegsedi) is a transthyretin-directed ASO medication approved by the FDA in 2018 for the management of damage of nerve in adults with hereditary transthyretin-mediated amyloidosis. It binds to transthyretin (TTR) mRNA causing degradation of mutant and wild-type TTR mRNA which results in a reduction of serum and tissue TTR protein. It is associated with severe adverse effects, such as, low platelet count and kidney inflammation. Because of these adverse effects, it is prescribed only through a restricted program called the Tegsedi risk evaluation and mitigation (REMS) program in the USA.³³

3.8. Neovascularization

A phase II study reported that eye drops of an ASO, aganirsen prevent insulin receptor substrate-1 expression and inhibit corneal neovascularization. In the phase III study, aganirsen eye drops extensively restrained corneal neovascularization in patients with keratitis. Hence, the option for transplantation is reduced for the treatment of viral keratitis and central neovascularization. The topical application of aganirsen was found to be secure and well-tolerated.³⁴

3.9. Arthritis

The treatment of arthritis is yet restricted to the utilization of analgesics and prosthetic replacement. Use of locked nucleic acid ASO ADAMTS5 (A Disintegrin and Metallo Proteinase with Thrombospondin Motifs)

showed 90% silencing in the monolayer culture of human OA chondrocytes. The ASO displayed a constant discharge profile with hydrogels up to 14 days determined by flow cytometry and confocal microscopy. This work displays the applicability of hydrogels for combined local delivery of ASOs for gene modulation.³⁵

3.10. Infectious Disease

Many antisense therapies are in evaluation in clinical trials for the treatment of numerous infectious diseases. MicroRNA-122 (miR-122) is believed to play an important role in inflammatory activity in the liver and RG-101, a GalNAc-conjugated oligonucleotide drug is developed to prevent replication of miR-122 and HCV. The outcomes from this clinical preliminary were tremendously reassuring and support continued investigation of the drug.³⁶

3.11. Vaccines

ASOs became the centre of research for improving the efficiency of vaccines because of high specificity. Several studies have reported improvement in the vaccines efficacy by ASOs either by inducing modifications in antigen or by targeting specific factors of the host immune system.³⁷

4. CONCLUSION

Antisense therapies in various disease conditions are empowering, yet safe delivery and long term efficacy of the treatment need to be determined. The enormous number of arranged and continuous clinical preliminaries in the antisense technology field mirrors the hopefulness of antisense ways to deal with direct quality articulation, miRNA pathways, and elective grafting to address hereditary diseases. It is predictable that the best achievements in this field to date have been in brain targeting and killing of tumors. Antisense therapeutics will be at the front line of clinical ways to deal with hereditary ailments later on. Antisense pharmaceuticals will soon be accessible for the standard consideration of patients and are hoped for being successful, effective specialists with positive restorative profiles in various disease conditions.

5. REFERENCES

- Samad MA, Pandiri K, Bojanapally AP. Antisense oligonucleotides: pharmacology and delivery strategies. *Int. J. Appl. Pharm. Sci. Res.* 2020;5(1):1-6.
- Evers mm, Toonen LJ, van Roon-Mom WM. Antisense oligonucleotides in therapy for neurodegenerative disorders. *Adv Drug Deliv Rev.* 2015;87:90-103.
- Crooke ST, Wang S, Vickers TA, Shen W, Liang XH. Cellular uptake and trafficking of antisense oligonucleotides. *Nat Biotechnol.* 2017;35(3):230-237.
- Karaki S, Paris C, Rocchi P. Antisense Oligonucleotides, A Novel Developing Targeting Therapy. *Antisense Therapy.* 2019. Available from: <https://www.intechopen.com/books/antisense-therapy/antisense-oligonucleotides-a-novel-developing-targeting-therapy>.
- Neuman BW, Stein DA, Kroeker AD, Paulino AD, Moulton HM, Iversen PL, Buchmeier MJ. Antisense Morpholino-Oligomers Directed against the 5' End of the Genome Inhibit Coronavirus Proliferation and Growth. *Journal of Virology.* 2004;78(11):5891-5899.
- Barrey EB, Dhorne-Pollet V, Eléouët S, Delmas JB. Think Different with RNA Therapy: Can Antisense Oligonucleotides Be Used to Inhibit Replication and Transcription of SARS-Cov-2?. *Preprints 2020, 2020040412.*
- Sadewasser A, Dietzel E, Michel S, et al. Anti-Niemann Pick C1 Single-Stranded Oligonucleotides with Locked Nucleic Acids Potently Reduce Ebola Virus Infection *In vitro*. *mol Ther Nucleic Acids.* 2019;16:686-697.
- Javanbakht H, Mueller H, Walther J, et al. Liver-Targeted Anti-HBV Single-Stranded Oligonucleotides with Locked Nucleic Acid Potently Reduce HBV Gene Expression *In vivo*. *mol Ther Nucleic Acids.* 2018;11:441-454.
- Markov AV, Kupryushkin MS, Goncharova EP et al. Antiviral Activity of a New Class of Chemically Modified Antisense Oligonucleotides against Influenza A Virus. *Russ J Bioorg Chem.* 2019;45:774-782.
- Ripple MJ, You D, Honnagowda S, et al. Immunomodulation with IL-4R alpha antisense oligonucleotide prevents respiratory syncytial virus-mediated pulmonary disease. *J Immunol.* 2010;185(8):4804-4811.
- Takahashi M, Li H, Zhou J, Chomchan P, Aishwarya V, Damha MJ, Rossi JJ. Dual Mechanisms of Action of Self-Delivering, Anti-HIV-1 FANA Oligonucleotides as a Potential New Approach to HIV Therapy. *molecular Therapy-Nucleic Acids.* 2019;17:615-625.
- Kim J, Hu C, Achkar cm, Black LE, Douville J, Larson A, et al. Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease. *New England Journal of Medicine.* 2019;381(17):1644-1652.
- Luo X, Fitzsimmons B, Mohan A, et al. Intrathecal administration of antisense oligonucleotide against p38α but not p38β MAP kinase isoform reduces neuropathic and postoperative pain and TLR4-induced pain in male mice. *Brain Behav Immun.* 2018;72:34-44.
- Friedrich J, Kordasiewicz HB, O'Callaghan B, Handler HP, Wagener C, Duvick L, Swayze EE, Rainwater O, Hofstra B, Benneyworth M, Nichols-Meade T, Yang P, Chen Z, Ortiz JP, Clark HB, Öz G, Larson S, Zoghbi HY, Henzler C, Orr HT. Antisense oligonucleotide-mediated ataxin-1 reduction prolongs survival in SCA1 mice and reveals disease-associated transcriptome profiles. *JCI insight.* 2018;3(21):e123193.
- Nguyen Q, Yokota T. Antisense oligonucleotides for the treatment of cardiomyopathy in Duchenne muscular dystrophy. *Am J Transl Res.* 2019 Mar 15;11(3):1202-1218.
- Finkbeiner S. Huntington's Disease. *Cold Spring Harb Perspect Biol.* 2011;3(6):a007476.
- Lane RM, Smith A, Baumann T, et al. Translating Antisense Technology into a Treatment for Huntington's Disease. *Methods mol Biol.* 2018;1780:497-523.
- Klim JR, Vance C, Scotter EL. Antisense oligonucleotide therapies for Amyotrophic Lateral Sclerosis: Existing and

- emerging targets. *Int J Biochem Cell Biol.* 2019;110:149-153.
19. Schoch KM, Miller TM. Antisense Oligonucleotides: Translation from Mouse Models to Human Neurodegenerative Diseases. *Neuron.* 2017;94(6):1056-1070.
 20. Cole TA, Zhao H, Collier TJ, Sandoval I, Sortwell CE, Steece-Collier K, . . . Paumier KL. Alpha-synuclein antisense oligonucleotides as a disease-modifying therapy for Parkinson's disease. 2019.
 21. Haché M, Swoboda KJ, Sethna N, *et al.* Intrathecal Injections in Children With Spinal Muscular Atrophy: Nusinersen Clinical Trial Experience. *J Child Neurol.* 2016;31(7):899-906.
 22. Aung-Htut MT, Comerford I, Johnsen R, Foyle K, Fletcher S, Wilton SD. Reduction of integrin alpha 4 activity through splice modulating antisense oligonucleotides. *Scientific reports.* 2019;9(1):12994.
 23. Que L, Claudette B, Esmat D, John G, Brett PM, Sanjay B. ISIS-FXIRx, A Novel and Specific Antisense Inhibitor of Factor XI, Caused Significant Reduction in FXI Antigen and Activity and Increased aPTT without Causing Bleeding in Healthy Volunteers. *Blood.* 2011;118(21):209.
 24. Phillips M, Costales J, Lee R, Oliveira E, Burns A. Antisense Therapy for Cardiovascular Diseases. *Current Pharmaceutical Design.* 2015;21(30):4417-4426.
 25. Wong E, Goldberg T. Mipomersen (kynamro): a novel antisense oligonucleotide inhibitor for the management of homozygous familial hypercholesterolemia. *P and T: a peer-reviewed journal for formulary management.* 2014;39(2):119-122.
 26. Guo S, Aghajan M, Casu C, Gardenghi S, Booten S, Rivella S, Monia BP. Targeting TMPRSS6 Using Antisense Technology for the Treatment of Beta-Thalassemia. *Blood.* 2015;126(23):753-753.
 27. Ball HA, Sandrasagra A, Tang L, Scott MV, Wild J, Nyce JW. Clinical Potential of Respirable Antisense Oligonucleotides (RASONS) in Asthma. *American Journal of Pharmacogenomics.* 2003;3(2):97-106.
 28. Liao W, Dong J, Peh HY, *et al.* Oligonucleotide Therapy for Obstructive and Restrictive Respiratory Diseases. *molecules.* 2017;22(1):139.
 29. Le BT, Raguraman P, Kosbar TR, Fletcher S, Wilton SD, Veedu RN. Antisense Oligonucleotides Targeting Angiogenic Factors as Potential Cancer Therapeutics. *mol Ther Nucleic Acids.* 2019;14:142-157.
 30. Hnik P, Boyer DS, Grillone LR, Clement JG, Henry SP, Green EA. Antisense oligonucleotide therapy in diabetic retinopathy. *J Diabetes Sci Technol.* 2009;3(4):924-30.
 31. Fefferman DS, Farrell RJ. Making sense of antisense: ISIS 2302 (alicaforfen) in the treatment of pouchitis. An enema formulation of alicaforfen, an antisense inhibitor of intercellular adhesion molecule-1, in the treatment of chronic, unremitting pouchitis. *Inflamm Bowel Dis.* 2004;10(4):487-8.
 32. Miner PB, Jr Geary RS, Matson J, Chuang E, Xia S, Baker BF, Wedel MK. Bioavailability and therapeutic activity of alicaforfen (ISIS 2302) administered as a rectal retention enema to subjects with active ulcerative colitis. *Aliment Pharmacol Ther.* 2006;23(10):1427-34.
 33. Mathew V, Wang AK. Inotersen: new promise for the treatment of hereditary transthyretin amyloidosis. *Drug Des Devel Ther.* 2019;13:1515-1525.
 34. Cursiefen C, Viaud E, Bock F, *et al.* Aganirsen antisense oligonucleotide eye drops inhibit keratitis-induced corneal neovascularization and reduce need for transplantation: the I-CAN study. *Ophthalmology.* 2014;121(9):1683-1692.
 35. Garcia JP, Stein J, Cai Y, *et al.* Fibrin-hyaluronic acid hydrogel-based delivery of antisense oligonucleotides for ADAMTS5 inhibition in co-delivered and resident joint cells in osteoarthritis. *J Control Release.* 2019;294:247-258.
 36. Bandiera S, Pfeffer S, Baumert TF, Zeisel MB. miR-122--a key factor and therapeutic target in liver disease. *J Hepatol.* 2015;62(2):448-457.
 37. Batista-Duharte A, Sendra L, Herrero MJ, Téllez-Martínez D, Carlos IZ, Aliño SF. Progress in the Use of Antisense Oligonucleotides for Vaccine Improvement. *Biomolecules.* 2020;10(2):316. Published 2020 Feb 17.

How to cite this article: Pandiri K, Samad MA, Gulamus NA, Khanam H. Medicinal applications of antisense oligonucleotides: a review. *Int J Appl Pharm Sci Res.* 2020;5(2): 30-36. doi: <https://doi.org/10.21477/ijapsr.5.2.2>

Source of Support: Nil.

Conflict of Support: None declared.