Neuropharmacology 120 (2017) 56–62

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Progress and promise of antisense oligonucleotide therapeutics for central nervous system diseases

Kathie M. Bishop, Ph.D.

Otonomy, 6275 Nancy Ridge Drive, San Diego, 92121, CA, USA

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form
15 November 2016
Accepted 16 December 2016
Available online 18 December 2016

Keywords:
Antisense oligonucleotides
Drug development
CNS diseases

ABSTRACT

Antisense oligonucleotide (ASO) drugs are an emerging class of therapeutics that have recently demonstrated progress and promise to treat diseases of the central nervous system (CNS). ASOs for a variety of targets and mechanisms are currently being investigated in clinical trials and pre-clinically for a number of CNS diseases. This review examines the available data regarding central ASO delivery, distribution, pharmacokinetics, pharmacodynamics and therapeutic opportunities.

This article is part of the Special Issue entitled “Beyond small molecules for neurological disorders”.

Contents

Antisense oligonucleotide (ASO) drugs are an emerging class of therapeutics designed to alter RNA expression and function, thus allowing the possibility for therapeutic intervention beyond protein or receptor engagement. Although antisense technology has a long history (Lundin et al., 2015), recently ASO drugs have demonstrated progress to treat diseases of the central nervous system (CNS). To date, five ASO therapeutics have entered clinical development (see Table 1). These include nusinersen for Spinal Muscular Atrophy (SMA), which recently reported positive results in two Phase 3 studies (NCT02292537 and NCT02193074; Kuntz, 2016; Ionis Pharmaceuticals press release, 2016), ISIS 333611 and BIIB067 for SOD1-related familial Amyotrophic Lateral Sclerosis (SOD1-fALS) in Phase 1/2 studies (Miller et al., 2013; NCT02623699), ISIS-HTT_{Rx} (ISIS 443139) for Huntington's disease (HD) in a Phase 1/2 study (NCT02519036), and trabedersen (AP 12009) for the treatment of high-grade gliomas (Jaschinski et al., 2011). Taken together, the initial preclinical and clinical data on the safety, feasibility, and efficacy of centrally applied ASO therapeutics indicate promise for the treatment of diseases of the brain and spinal cord and have provided informative data for the

E-mail address: kbishop@otonomy.com.

http://dx.doi.org/10.1016/j.neuropharm.2016.12.015
0028-3908/

Table 1
Antisense oligonucleotide therapeutics in clinical development for CNS diseases.

ASO	Disease	Target	Chemistry	Mechanism	Target cells	Dose administration	Phase of Development
nusinersen (ISIS 396443; ISIS-SMN_{Rx})	Spinal muscular atrophy	*SMN2* pre-mRNA	PS 2′-MOE modification	splice modification	spinal cord and brain motor neurons	Intrathecal bolus injection	Phase 3 in infants positive Phase 3 in children positive
ISIS 333611	SOD1-related familial ALS	*SOD1* mRNA	PS 2′-MOE modification	RNase H mediated degradation	spinal cord and brain motor neurons	Intrathecal infusion	Phase 1 completed
BIIB067	SOD1-related familial ALS	*SOD1* mRNA	PS modification unknown	RNase H mediated degradation	spinal cord and brain motor neurons	Intrathecal bolus injection	Phase 1/2 ongoing
ISIS-Htt_{Rx} (ISIS 443139)	Huntington's disease	*HTT* mRNA	PS 2′-MOE modification	RNase H mediated degradation	striatal and cortical neurons	Intrathecal bolus injection	Phase 1/2 ongoing
trabedersen (AP 12009)	High-grade gliomas	*TGF-β2* mRNA	PS modification unknown	RNase H mediated degradation	glioma tumor tissue	Intratumoral infusion	Phase 3 discontinued

development of future therapeutics. Consequently, ASOs are currently being investigated pre-clinically for a number of CNS diseases utilizing a variety of targets and mechanisms. This review examines the available data regarding central ASO delivery, distribution, pharmacokinetics, pharmacodynamics and therapeutic opportunities. It focuses on therapeutic applications of ASOs; the additional broad research use of ASOs to investigate mechanisms of CNS diseases and therapeutic targets is not discussed.

1. ASO drug overview

Antisense oligonucleotides are short strands of synthetic DNA-like molecules, usually between 13 and 25 nucleotides long, and are classified as chemicals per drug development regulations. These compounds bind to RNA with high affinity and selectivity through well-characterized Watson-Crick base pairing (hybridization). Several different chemistries for ASOs are being developed (Evers et al., 2015), most of which contain a phosphorothiorate (PS) linkage backbone plus 2'-ribose sugar modifications (2′-MOE, 2′-OMe, cEt, LNA, 2′-Fluoro) or sugar-phosphate modifications (PNA, morpholino). These chemical modifications have enabled development of ASO compounds with improved nuclease resistance, greater potency, and lessened toxicities. Mechanistically, ASOs can modulate RNA in many different ways (reviewed in Bennett and Swayze, 2010). The most commonly utilized mechanism is that of RNA degradation or 'knockdown', which results in the selective reduction of the RNA and, if applicable, the downstream protein of interest. This mechanism acts through recruiting the endogenous enzyme RNase H to the ASO/RNA complex and requires a stretch of unmodified DNA in the middle of the ASO molecule to provide a substrate for RNase H binding (Bennett and Swayze, 2010). Another well-characterized ASO mechanism is that of 'splice modification' in which fully modified ASOs targeting the pre-mRNA induce switching between alternative splice isoforms through exon skipping (Siva et al., 2014). Importantly, ASOs can target RNA in the nucleus and/or in the cytoplasm and are capable of modulating many forms of RNA (mRNA, pre-mRNA, toxic RNA sequestered in the nucleus, non-coding RNA, microRNA, etc.). Thus, the design of the ASO is selected in accordance with the known mechanism of the disease targeted and the sequence of the target RNA. With regards to the treatment of CNS diseases, further optimization of the chemistry and design is required to optimize CNS tolerability and pharmacology. Taken together, rigorous chemical design and screening of ASOs are critical for successful drug development; however, a platform technology such as ASOs has the potential advantage of reducing timelines and costs for drug discovery and increasing the chances of success by building on platform knowledge (Bennett, 2002). ASO drugs are water-soluble and are chemically stable for years with refrigeration. ASO drugs are easily formulated in phosphate buffer, but for CNS applications formulation in artificial cerebral spinal fluid (CSF) is recommended to improve tolerability with central delivery. ASOs are considered chemicals from a regulatory perspective as they are manufactured using a chemical synthesis process that is generally straightforward and is cost effective compared to biologics manufacturing.

2. CNS pharmacokinetics and pharmacodynamics

Antisense oligonucleotides do not readily cross the intact blood-brain barrier (Smith et al., 2006) and thus to be effective in brain and spinal cord tissues must be delivered centrally. In clinical studies conducted to date, this has been achieved through intrathecal bolus injection (Chiriboga et al., 2016; Haché et al., 2016; NCT02623699; NCT02519036), intrathecal continuous infusion (Miller et al., 2013), and intratumoral infusion into gliomas (Bogdahn et al., 2011). In preclinical animal models, intraventricular injections or infusions and intraparenchymal delivery have also been utilized. Once delivered into the circulating CSF, ASOs readily distribute broadly throughout the CNS tissues, with the highest concentrations achieved in tissues most proximal to the CSF and lower concentrations most distal to CSF sources along a gradient (Kordasiewicz et al., 2012; Rigo et al., 2014). In general, this means that following intrathecal delivery in larger primate brains, the spinal cord, cortex, cerebellum, hippocampus, and areas of the caudate proximal to the ventricle have highest concentrations and the deeper areas of the brain the lowest (Kordasiewicz et al., 2012; Rigo et al., 2014). ASOs are actively taken up within neurons, glia, and other cell types within the brain and spinal cord and do not seem to exhibit cell-type specificity (Butler et al., 2005; Whitesell et al., 1993).

Following intrathecal bolus injection, peak CSF concentrations are observed within 30–60 minutes after dosing and then rapidly decline over the next 24–48 hours (Miller et al., 2013; Chiriboga et al., 2016) due to distribution to CNS tissues and also transfer of a portion of the dose to the systemic circulation with CSF turnover. Plasma concentrations peak within about 2–5 hours after dosing,