MILESTONE 5

First antisense drug is approved with fleeting success

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Following the initial reports and characterization of gene silencing through endogenous and exogenous antisense RNAs, the first antisense oligonucleotide drug, fomivirsen, received regulatory approval from the United States Food and Drug Administration (FDA) in 1998. This agent was indicated for the treatment of cytomegalovirus (CMV) retinitis — a serious infection of the retina that can rapidly lead to blindness — in carriers of human immunodeficiency virus (HIV) exhibiting acquired immune deficiency syndrome (AIDS), who were intolerant of, or had contraindications to, other treatments or were insufficiently responsive to previous treatments. Fomivirsen was subsequently granted marketing authorisation by the European Medicines Agency (EMA; formerly the EMEA) for the same indication in 1999.

Fomivirsen is a synthetic 21-nucleotide phosphorothioate oligodeoxynucleotide designed to be complementary to a sequence in CMV mRNAs encoding the major immediate-early region 2 proteins, which are essential for CMV replication. In line with this antisense mechanism of action, early preclinical characterization revealed that fomivirsen potently and selectively disrupted CMV replication in a dose-dependent manner in vitro, providing the first indication of its efficacy.

Regulatory approval was largely based on three prospective randomized controlled trials (RCTs) led by the Vitravene Study Group, which demonstrated the efficacy of fomivirsen for the treatment of CMV retinitis in individuals with AIDS. In a pivotal phase III RCT, patients with newly diagnosed CMV retinitis were randomly allocated to immediate intravitreal fomivirsen treatment or treatment deferral until progression. Median time to progression was 71 days in the immediate treatment group, versus 13 days in the deferred treatment group. Progression after treatment cessation occurred in 44% of patients receiving immediate treatment, versus 70% of patients in the deferred treatment group. Two additional RCTs demonstrated the comparable efficacy of an intensive and less-intensive regimen of intravitreal fomivirsen for the treatment of CMV retinitis that had not been controlled by other drugs.

However, despite the initial enthusiasm and unmet clinical need in the late 1990s, the success of fomivirsen was ultimately fleeting. The drug was withdrawn by the FDA in 2001, owing to the success of highly active antiretroviral therapy in reducing the incidence of opportunistic infections in individuals with HIV in the early 2000s, which undermined demand for fomivirsen. The EMA followed suit in 2002, when the manufacturer (Novartis) voluntarily withdrew the drug from the market due to low demand.

Nevertheless, the success of fomivirsen provided proof-of-concept of the clinical promise of treatments based on antisense oligonucleotides, which was undoubtedly valuable for the next wave of antisense drug approvals, beginning in 2013 with the FDA approval of mipomersen (an antisense oligonucleotide inhibitor of apolipoprotein B) for the treatment of homozygous familial hypercholesterolemia.

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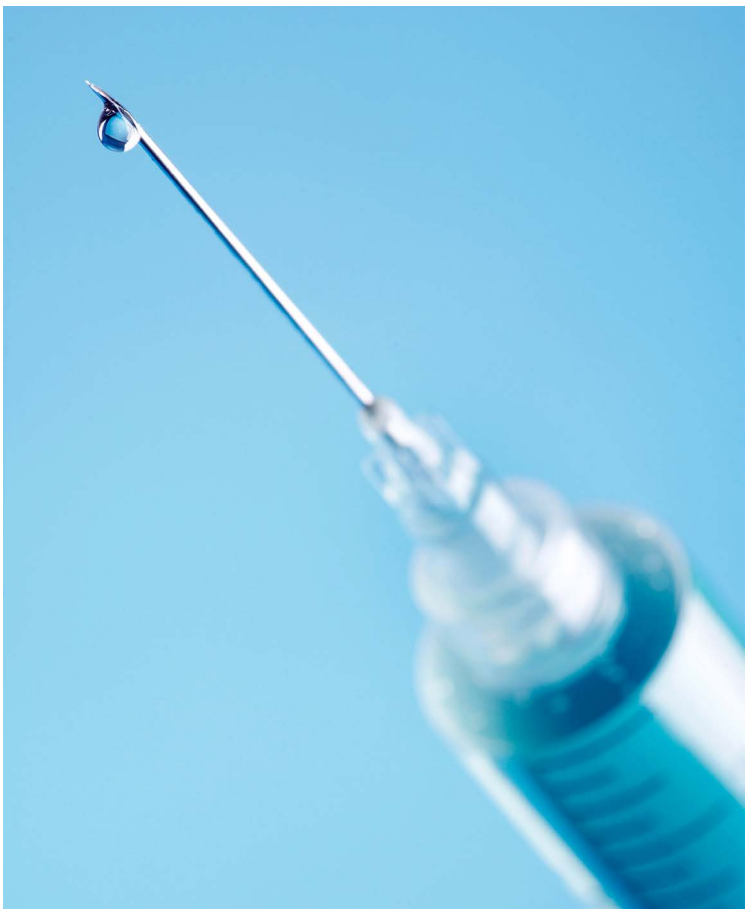

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FURTHER READING *Drug Approval Package: Vitravene* (US FDA, 2002); https://go.nature.com/2kfsM3N | *Vitravene* (EMA, 2002); https://go.nature.com/2kJcOze | Vitravene Study Group. A randomized controlled clinical trial of intravitreous fomivirsen for treatment of newly diagnosed peripheral cytomegalovirus retinitis in patients with AIDS. *Am. J. Ophthalmol.* **133**, 467–74 (2002) | Vitravene Study Group. 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.* **133**, 475–83 (2002).