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Fomivirsen

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Contents

Abstract

▲ Fomivirsen (ISIS 2922) is an antisense oligonucleotide which specifically inhibits replication of human cytomegalovirus. It achieves this by binding to complementary sequences on messenger RNA transcribed from the major immediate-early transcriptional unit of the virus. It is being developed for the treatment of cytomegalovirus retinitis.

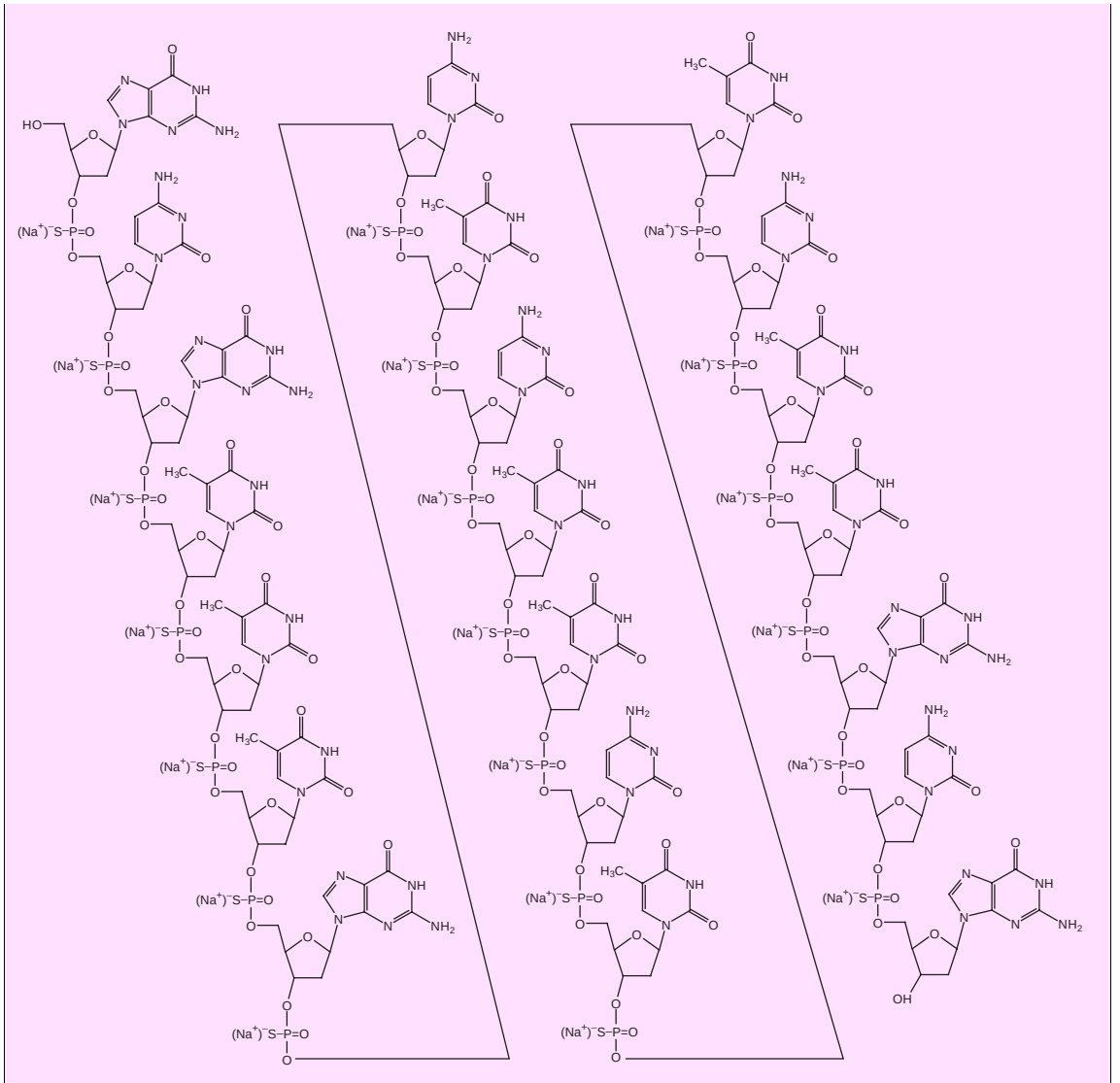
▲ Mean maximum retinal concentrations of fomivirsen occurred ≈2 days after a single intravitreal injection in monkeys. The elimination half-life of fomivirsen (after a single 115μg dose) in monkey retina was 78 hours.

▲ Fomivirsen, administered as an intravitreal injection, significantly delayed progression of cytomegalovirus retinitis in patients with AIDS in preliminary clinical trials. In 18 patients with newly diagnosed, unilateral, peripheral cytomegalovirus retinitis treated with fomivirsen 165μg once weekly for 3 weeks, then 165μg every second week, the median time to disease progression was significantly longer than in 10 patients in whom fomivirsen treatment was deferred until early disease progression (71 *vs* 14 days).

▲ In patients with advanced, refractory, sight-threatening disease, treatment with fomivirsen 330μg once weekly for 3 weeks and then 330μg every 2 weeks (n = 34) or 330μg on days 1 and 15 and then monthly (n = 20) significantly delayed disease progression. The interpolated median time to disease progression was 90 days in both treatment groups.

▲ The most common adverse events reported in clinical trials of fomivirsen were increased intraocular pressure and mild to moderate intraocular inflammation. These events were generally transient or reversible with topical steroid treatment.

Features and properties of fomivirsen (ISIS 2922)	
Indications	
Treatment of cytomegalovirus retinitis in patients with AIDS	Phase III; approved
Mechanism of action	
Antiviral	Antisense oligonucleotide
Dosage and administration	
Usual dosage in clinical trials	165μg weekly for 3 weeks, then 165μg every 2 weeks in patients with newly diagnosed cytomegalovirus retinitis; 330μg weekly for 3 weeks or 330μg every other week for 2 doses then 330μg every 2 or 4 weeks in patients with advanced, refractory, sight-threatening disease
Route of administration	Intravitreal injection
Pharmacokinetic profile	
Peak concentration in retina	3.5 μmol/L after a single 66μg intravitreal injection (in rabbits)
Time to peak concentration in retina	2-5 days (in animals)
Elimination half-life in retina	78-79 hours (in animals)
Adverse events	
Most frequent	Increased intraocular pressure and mild to moderate intraocular inflammation
Serious events	Marked retinal toxicity in a recipient of fomivirsen 495μg



Fomivirsen (ISIS 2922)

Human cytomegalovirus, a ubiquitous herpesvirus, is the most common cause of viral retinitis in immunocompromised individuals, including patients with HIV infection.[1] Cytomegalovirus retinitis is a sight-threatening disease, characterised by the progressive destruction of retinal cells, and is a major cause of morbidity in patients with AIDS.[1,2]

Antisense oligonucleotides are synthetic, short, single-stranded sequences of DNA or RNA that are designed to target and bind to messenger RNA, thus disrupting gene expression and inhibiting protein synthesis.[3,4] Fomivirsen (ISIS 2922) is the first drug of this class to be evaluated in the treatment of patients with AIDS-related cytomegalovirus retinitis.

1. Pharmacodynamic Profile

Antiviral Activity

- Fomivirsen is a novel antisense phosphorothioate oligonucleotide, which binds to complementary sense sequences on messenger RNA transcribed from the major immediate-early transcriptional unit of human cytomegalovirus.[5,6] By inhibiting the functioning of this unit, fomivirsen is able to produce specific and potent inhibition of human cytomegalovirus replication without interfering with the functioning of human genes.[5-7]

- The antiviral mechanism of action of fomivirsen is complex.[6] In cell culture assays, antisense and nonantisense mechanisms appeared to contribute to the antiviral activity of the drug.[6] These included inhibition of cytomegalovirus immediate-early gene expression (a sequence-dependent antisense mechanism) which is essential for virus replication and inhibition of adsorption of cytomegalovirus to host cells (a sequence-independent mechanism).[5,6]

- Fomivirsen-mediated reduction of immediate-early protein synthesis in human cytomegalovirus-infected normal human dermal fibroblast (NHDF) cells occurred in a dose-dependent manner.[5]

- Fomivirsen is active *in vitro* against clinical isolates of human cytomegalovirus and against drug-resistant mutants of the virus.[6] In cell culture, the mean 50% effective concentration (EC_{50}) of fomivirsen against the AD169 strain of human cytomegalovirus was 0.37 μmol/L. The EC_{50} of fomivirsen was 30 to 90 times lower than that of ganciclovir against this strain of human cytomegalovirus.[5]

- At concentrations of 2.2 and 36 μmol/L, respectively, fomivirsen and ganciclovir produced 99% inhibition of infectious human cytomegalovirus production in NHDF cells in an infectious yield reduction assay.[5]

- Combinations of fomivirsen and ganciclovir or foscarnet showed additive antiviral activity against human cytomegalovirus in cell culture assays.[8] Additive antiviral activity was also observed with fomivirsen in combination with a high concentration (300 μmol/L) of dideoxycytidine, but was not evident when fomivirsen was combined with lower concentrations of this agent.[8]

- In cell culture assays, zidovudine showed no significant activity against human cytomegalovirus. The antiviral activity of fomivirsen was not altered when the drug was used in combination with zidovudine *in vitro*.[8]

Resistance

- A human cytomegalovirus mutant (designated 2922^{r}A-32-1) resistant to fomivirsen was isolated after passage of human fibroblast cells infected with human cytomegalovirus (derived from a wild-type laboratory strain of AD169) in fomivirsen at concentrations of 16 and 32 μmol/L. The mutant was 10-fold less susceptible to fomivirsen than the parental strain AD169 (EC_{50} 700 *vs* 70 nmol/L).[9]

- Sequencing of 2922^{r}A-32-1 showed no changes in the region of the genome complementary to fomivirsen, indicating that viral resistance was not caused by an alteration in the encoded region with complementarity with fomivirsen.[9]

- The mutant showed cross-resistance to ISIS 13312, a derivative of fomivirsen with a base sequence identical to that of the parent drug.[9] In contrast, little or no cross-resistance was observed between fomivirsen and ISIS 3383, a phosphorothioate oligonucleotide with a base sequence different from that of fomivirsen.[9]

2. Pharmacokinetic Profile

- The pharmacokinetics of fomivirsen after intravitreal injection have been studied in rabbits and cynomolgus monkeys. Four hours after intravitreal injection of single 66μg doses of [^{14}C]-labelled fomivirsen to rabbits, the mean concentration of fomivirsen in vitreous humour was 3.3 μmol/L (fig. 1).[10]

- Elimination of the drug from vitreous humour was slow and appeared to follow first-order kinetics. The elimination half-life ($t_{½}$) of fomivirsen in vitreous humour was 62 hours.[10]

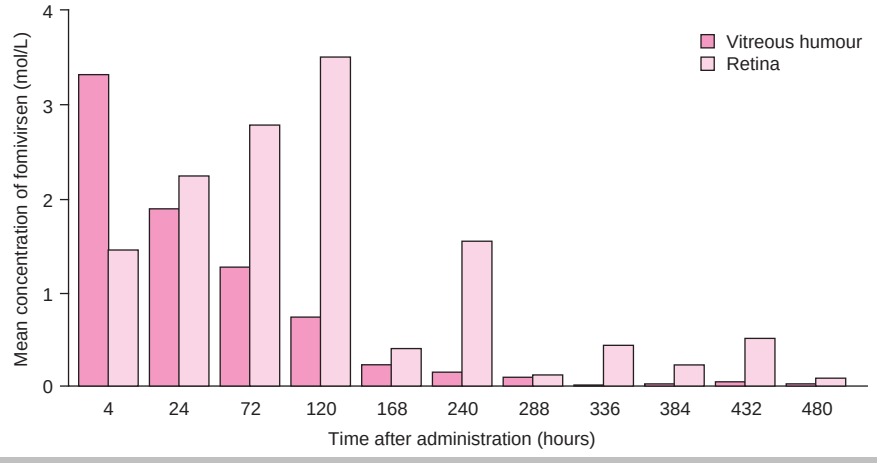


Fig. 1. Mean concentrations of fomivirsen in rabbit vitreous humour and retina after single intravitreal injections of fomivirsen 66μg.[10]

• Ten days after administration, the mean concentration of fomivirsen in rabbit vitreous humour (0.17 μmol/L) [fig. 1] was still within the range of concentrations shown to inhibit human cytomegalovirus replication in *in vitro* cell culture studies.[5,10]

• At this time-point, 22% of the total radioactivity detected in vitreous humour represented fomivirsen. Chain-shortened metabolites of the parent drug appeared to constitute the remaining 78% of radioactivity, suggesting that fomivirsen undergoes extensive metabolism within the vitreous humour.[10]

• Concentrations of fomivirsen in rabbit retina increased and declined more gradually than in the vitreous humour. A maximum concentration of 3.5 μmol/L was achieved in the retina 5 days after administration of a single 66μg intravitreal injection of the drug (fig. 1).[10] Ten days after administration, the mean retinal concentration of fomivirsen was almost 10 times higher than that in the vitreous humour (1.6 *vs* ≈0.17 μmol/L) [fig. 1]. The estimated $t_{½}$ of fomivirsen in the retina was 79 hours.

• In cynomolgus monkeys, concentrations of fomivirsen in the vitreous humour increased in a dose-proportional and almost linear manner after intravitreal injection of single doses of 11, 57 or 115μg per eye.[11] Maximum retinal concentrations of fomivirsen (ranging from 50 nmol/L to 1.1 μmol/L) were achieved ≈2 days after administration.[11] Three days after injection, concentrations of fomivirsen in the vitreous humour ranged from 80 nmol/L to ≈1.5 μmol/L. Fomivirsen was undetectable in the vitreous humour 14 days after administration.

• There was no evidence of accumulation of fomivirsen in the vitreous humour of monkeys after multiple weekly or biweekly doses of 11, 57 or 115μg per eye.[11] However, accumulation of fomivirsen occurred in the retina after multiple doses of 57μg weekly or 115μg every 2 weeks, suggesting that mechanisms for clearing the drug had been saturated during multiple dose administration.[11] The elimination half-life of fomivirsen (after a single 115μg dose) in monkey retina was 78 hours.

3. Therapeutic Trials

Previously Untreated Patients

• In clinical trials of fomivirsen conducted in patients with AIDS and cytomegalovirus retinitis, treatment efficacy was determined by 'masked' assessment of retinal photographs.

• Treatment with fomivirsen significantly delayed progression of cytomegalovirus retinitis in 18 patients with AIDS and newly diagnosed unilat-

eral peripheral cytomegalovirus retinitis compared with 10 similar patients in whom treatment with the drug was deferred until disease progression (as defined by standard criteria) had occurred (median time to progression 71 vs 14 days) [intention-to-treat analysis] $p \leq 0.005$ (fig. 2).[12,13]

- In both groups, fomivirsen was given by intravitreal injection at a dosage of 165µg once weekly for 3 weeks then 165µg every second week as maintenance therapy.[14]

Previously Treated Patients

- Fomivirsen decreased cytomegalovirus activity (assessed by masked reading of retinal photographs) in patients with AIDS and refractory cytomegalovirus retinitis in a phase I dose-ranging study.[15] Of the 22 patients (28 affected eyes) included in the study, some (number not reported) received intravitreal injections of fomivirsen 83, 165, 330 or 495µg per week for 3 weeks (induction therapy) and then every second week (maintenance therapy). The remaining patients received intravitreal fomivirsen 330µg every second week from treatment initiation.[15]

- A dose-response relationship was observed in the above dose-ranging study; decreased cytomegalovirus activity was observed in 0 of 2, 2 of 4 and 6 of 10 eyes treated with the 83, 165 and 330µg dosage regimens, respectively. Seven of 11 eyes treated with 330µg every second week from the initiation of therapy also responded to treatment.[15]

- A significant delay in disease progression occurred in 54 previously-treated patients with advanced, sight-threatening cytomegalovirus retinitis who received intravitreal injections of fomivirsen 330µg weekly (given with local anaesthesia[7]) for 3 weeks and then every second week as maintenance therapy (n = 34) or 330µg on days 1 and 15, and then monthly (n = 20).[7, 16-18] Interpolated median time to disease progression was 90 days with both regimens.[18] Evidence of decreased border opacification (a clinical response) was observed a median of 8 days after treatment initiation in both groups.[7,16]

4. Tolerability

- Increased intraocular pressure and mild to moderate intraocular inflammation of the anterior and posterior chambers were the most common adverse events reported in clinical trials of fomivirsen conducted in patients with AIDS-related cytomegalovirus retinitis.[12,15,16,18] Both events were generally transient or reversible with topical steroid treatment.[15,18]

- Incidences of increased intraocular pressure and of inflammation of the anterior ocular chamber were 18.5 and 15%, respectively, in 28 patients with newly diagnosed AIDS-related cytomegalovirus retinitis who received fomivirsen (165µg weekly for 3 weeks then 165µg every second

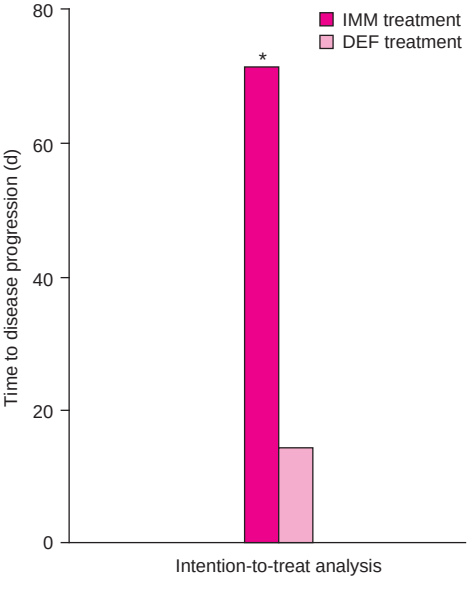


Fig. 2. Time to progression of cytomegalovirus retinitis in patients with AIDS-related cytomegalovirus retinitis receiving treatment with fomivirsen (intention-to-treat analysis). Patients either received immediate fomivirsen treatment (IMM treatment group) [n = 18] or had treatment deferred until a diagnosis of early disease progression (DEF treatment group) [n = 10].[12,13] In both groups, fomivirsen was given by intravitreal injection at a dosage of 165µg weekly for 3 weeks (induction therapy) then 165µg biweekly as maintenance therapy.[14] * $p \leq 0.005$ *vs* DEF group.

week[14]) as first-line therapy.[12-14] Neither retinal detachment nor evidence of systemic toxicity was observed in any of the study participants.[12]

- In patients with advanced, sight-threatening, refractory cytomegalovirus retinitis, fomivirsen 330μg on day 1, day 15 and monthly thereafter (n = 20) was better tolerated than a more intensive regimen [330μg weekly for 3 weeks then 330μg every second week (n = 34)].[18] Combined incidences of intraocular inflammation and increased intraocular pressure in the low and high dosage groups were 10 to 12% and 20%, respectively.[18]
- Pooled data from the manufacturer's database showed that the most common adverse events in 330 patients (433 eyes) with AIDS-related cytomegalovirus retinitis treated with fomivirsen (dosage not reported) were increased intraocular pressure (12 to 20%), anterior chamber inflammation (10 to 20%), cataracts (7 to 14%), vitritis (10 to 12%) and uveitis (5 to 10%).[16]
- Marked retinal toxicity was observed in the only recipient of intravitreal fomivirsen 495μg in a dose-ranging trial.[15] A small number of patients have developed peripheral retinal pigment epithelial stippling during treatment with the drug.[19]

5. Fomivirsen: Current Status

Fomivirsen is an antisense oligonucleotide which inhibits replication of human cytomegalovirus. It is in late clinical development and has been approved for the second-line treatment of cytomegalovirus retinitis in patients with AIDS who are intolerant of or unresponsive to previous treatment(s) for the disease.[20] Fomivirsen should not be administered to patients who have received treatment with cidofovir 2 to 4 weeks previously because of the increased risk of intraocular inflammation in such patients.[21]

References

1. Nokta MA, Hausrath SG, Pollard RB. Emerging treatments for viral retinitis. Biodrugs 1997 Jun; 7: 423-32
2. Temsamani J, Pari GS, Guinot P. Antisense approach for the treatment of cytomegalovirus infection. Expert Opin Invest Drug 1997 Sep; 6: 1157-67
3. Bonn D. Prospects for antisense therapy are looking brighter [news]. Lancet 1996 Mar 23; 347: 820
4. Fraser GL, Wahlestedt C. Applications of antisense technology to both basic and clinical research. Expert Opin Invest Drug 1995; 4 (7): 637-46
5. Azad RF, Driver VB, Tanaka K. Antiviral activity of a phosphorothioate oligonucleotide complementary to RNA of the human cytomegalovirus major immediate-early region. Antimicrob Agents Chemother 1993 Sep; 37: 1945-54
6. Anderson KP, Fox MC, Brown-Driver V, et al. Inhibition of human cytomegalovirus immediate-early gene expression by an antisense oligonucleotide complementary to immediate-early RNA. Antimicrob Agents Chemother 1996 Sep; 40: 2004-11
7. Henahan S. Fomivirsen focuses on the future in CMV retinitis. Inpharma 1998 May 23; 1138: 11
8. Azad RF, Brown-Driver V, Buckheit JRW, et al. Antiviral activity of a phosphorothioate oligonucleotide complementary to human cytomegalovirus RNA when used in combination with antiviral nucleoside analogs. Antiviral Res 1995 Oct; 28: 101-11
9. Mulamba GB, Hu A, Azad RF, et al. Human cytomegalovirus mutant with sequence-dependent resistance to the phosphorothioate oligonucleotide fomivirsen (ISIS 2922). Antimicrob Agents Chemother 1998 Apr; 42: 971-3
10. Leeds JM, Henry SP, Truong L, et al. Pharmacokinetics of a potential human cytomegalovirus therapeutic, a phosphorothioate oligonucleotide, after intravitreal injection in the rabbit. Drug Metab Dispos 1997 Aug; 25: 921-6
11. Leeds JM, Henry SP, Bistner S, et al. Pharmacokinetics of an antisense oligonucleotide injected intravitreally in monkeys. Drug Metab Dispos 1998 Jul; 26: 670-5
12. Johnson DW, Muccioli C, Goldstein DA, et al. Safety and efficacy of fomivirsen in the treatment of CMV retinitis: a phase 3, controlled, multicenter study comparing immediate versus delayed treatment [abstract]. 8th International Congress on Infectious Diseases; 1998 May 15-18; Boston, 135
13. Muccioli C, Goldstein DA, Johnson DW, et al. Fomivirsen safety and efficacy in the treatment of CMV retinitis: a phase 3, controlled, multicenter study comparing immediate versus delayed treatment [abstract]. 5th Conference on Retroviruses and Opportunistic Infections; 1998 Feb; Chicago, 224
14. Isis Pharmaceuticals, Carlsbad, California. 1998 (Data on file)
15. Hutcherson SL, Palestine AG, Cantrill HL, et al. Antisense oligonucleotide safety and efficacy for CMV retinitis in AIDS patients [abstract]. 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17; San Francisco, 204
16. Isis *Vitravene* may be considered for first-line use in CMV retinitis. The Pink Sheet 1998 Jul 27: 5
17. ISIS and CIBA vision present positive phase III results for antisense CMV retinitis drug advanced disease trial results support earlier findings; NDA submission imminent . Newswire; http:/wwwnewspagecom 1998
18. FDA panel supports Isis's antisense drug. Scrip Mag 1998 Jul 29 (2356): 22
19. Hudson HL, Boyer DS, Kupperman BD. Future trends and experimental modalities in the therapeutics of cytomegalovirus retinitis. Ophthal Clin North Am 1997; 10 (1): 61-71
20. Isis/Ciba Antisense Compound *Vitravene* approved for CMV retinitis. The Pink Sheet 1998 Aug 31: 27
21. Isis Pharmaceuticals USA. Fomivirsen sodium prescribing information. 1998

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