The Novel Antiviral Pipeline to Treat Severe Neonatal Viral Infections

Seilesh Kadambari, MRCPCH,* Paul D. Griffiths, FRCPath,† and Mike Sharland, FRCPCH*

From the *Paediatric Infectious Diseases Research Group, Jenner Wing, St George’s University of London; and †centre for Virology, University College London Medical School Royal Free Hospital, Rowland Hill Street, London, United Kingdom. The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Kadambari S, Paediatric Infectious Diseases Research Group, Jenner Wing, St George’s University of London, Cranmer Terrace, London SW17 0RE. E-mail: skadamba@sgul.ac.uk.
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It is likely that the number of viral infections detected will increase as molecular diagnostic laboratory techniques replace traditional culture methods, and so a decline in the pharmaceutical industry’s pipeline of novel antiviral agents is of significant concern. Neonates are more susceptible to disseminated viral diseases, such as herpes simplex virus (HSV), cytomegalovirus (CMV) and enteroviruses (EV), as a result of immature cellular and humoral immune responses and physical barriers to infection. Nucleoside analogues such as acyclovir, ganciclovir and their oral prodrugs valacyclovir and valganciclovir are the mainstay of treatment of neonatal HSV and CMV disease. Many nucleoside analogues are associated with toxicity and emerging resistance in the immunocompromised.

We could identify no current clinical trials of antivirals against EV infection, and no specific therapy is licensed for EV infections. Motavizumab, a respiratory syncytial virus (RSV) monoclonal antibody, has been recently discontinued by AstraZeneca (Gaithersburg, Maryland) after phase 3 trials due to Food and Drug Administration concerns regarding its limited efficacy and frequency of recorded hypersensitivity reactions.1 Aplylam-RSV01, an RNA interference agent that acts by targeted cleavage of messenger RNA, has been shown in a phase 2b trial to be safe and improve symptoms in RSV-infected lung transplant patients.2 However, we could identify no other agents targeting RSV or adenovirus entering phase 3 trials. There have been recent advances in treatment strategies for antiviral agents for HIV and influenza, which are not included here.3,4

This focused review explores novel antivirals in the pharmaceutical pipeline according to their mechanism of action and identifies the gaps for potentially fatal severe neonatal viral infections.

NON-NUCLEOSIDE DRUGS

Viral Helicase–Primase Complex Inhibitor: AIC316

Helicases are a group of enzymes that act to separate strands of a DNA double helix prior to copying DNA and help, in part, to regulate RNA transcription and translation. AIC316 has a unique method of stopping viral replication by targeting the viral helicase case involved in DNA replication. A phase 2 double-blind placebo-controlled dose-ranging study in adults showed a significant and dose-dependent reduction in the rate of viral shedding and clinical symptoms in HSV-2-infected patients receiving AIC316 (http://www.clinicaltrials.gov/ct2/show/NCT01047540?term =AIC+316&rank=2). One hundred fifty-six immunocompetent HSV-2 seropositive adults with a history of recurrent genital herpes were recruited across the United States in 2010. Subjects were randomized to 1 of 5 different groups. Treatment was administered orally for 4 weeks: 5 mg once daily (od), 25 mg od, 75 mg od, 400 mg once weekly, or matching placebo. The majority of participants in the 75-mg od group had no HSV DNA shedding, and trough concentrations of >2500 ng/mL were recorded. Resistant strains did not emerge in any of the 823 positive swabs, which underwent DNA sequence analysis for the most common gene mutations.

Viral Helicase–Primase Complex Inhibitor: ASP2151

ASP2151 (amenavir) has potent in vitro and in vivo activity against HSV and varicella zoster. A double-blind, multicenter, randomized, active- and placebo-controlled phase 2 study recently recruited 432 participants across 26 sites in the United States.5 The authors demonstrated that 4 different dose regimens of ASP2151 administered for acute treatment of recurrent genital herpes resulted in shorter median lesion duration by about a day in comparison with placebo. The drug was well tolerated with minor gastrointestinal upset reported. ASP2151 may provide a treatment alternative for immunocompromised participants who have infection with HSV that is resistant to nucleoside analogues.

Human Cytomegalovirus Terminase Inhibitor: AIC246

The viral terminase complex of human cytomegalovirus (HCMV) cleaves and...
packages single length genomes into a viral capsid. AIC246 (letermovir) has been shown in in vitro and in vivo studies to disrupt the viral terminase complex of HCMV and not the viral DNA polymerase, which antivirals on the market currently target. A recent randomized, double-blind placebo-controlled phase 2b study assessed the incidence and time to onset of HCMV prophylaxis failure (CMV viremia or antigenemia) and population pharmacokinetics of administering oral AIC246 at 60mg, 120mg or 240mg od or placebo for 84 days to 132 HCMV seropositive allogeneic human blood precursor cell transplant recipients after engraftment (http://www.clinicaltrials.gov/ct2/show/NCT01063829?term=AIC246&r=1). AIC246 was shown to have a failure rate significantly lower at a dose of 240 mg od (29.4%; P = 0.007) and 120 mg od (32.3%; P = 0.014) than placebo (63.6%). Prophylaxis failure was reported in only 2 (5.9%) patients with AIC246 240 mg od versus 12 (36.4%) with placebo. Only 2 patients experienced adverse events when taking AIC246 240 mg compared with 11 (33.3%) who took placebo. AIC246 has been granted Orphan Drug Designation in the European Union and the Food and Drug Administration since December 2011 for the prevention of HCMV viremia and disease in at-risk populations.

Lipid Conjugate of Cidofovir: CMX001

CMX001 is a broad spectrum lipid acyclic nucleoside phosphonate that is converted intracellularly into the active antiviral cidofovir diphosphate. CMX001 has in vitro activity against all double-stranded DNA viruses. CMX001 does not require phosphorylation by the HSV thymidine kinase and so should be effective against acyclovir-resistant infections. Observational data collected from 75 children treated with CMX001 as an Emergency Investigational New Drug application included 56 (75%) transplant recipients infected with adenovirus (63%), CMV (29%) and HSV (19%). The median (range) duration of CMX001 dosing was 35 (1–214) days in children and at a median twice weekly dose of 3.8 mg/kg. Uncontrolled data from this study highlighted no effect on renal function and no liver or hematological toxicity. Data from a series of animal models showed that the efficacy of CMX001 when given synergistically with acyclovir for the treatment of HSV infection is improved without apparently increasing toxicity. The Collaborative Antiviral Study Group will be recruiting into a randomized dose-finding study of CMX001 in infants with neonatal HSV (http://www.clinicaltrials.gov/ct2/show/NCT01610765?term=CMX001&rank=1). The 18 center study will recruit infants with virological confirmation and central nervous system involvement. Subjects will be given 21 days of IV acyclovir (as standard of care), and all subjects will receive in addition 1 of the 4 CMX001 treatment groups: 0.25, 0.5, 1.0 or 2.0 mg/kg/dose given orally twice a week for 3 weeks with a 3:1 ratio of active drug to matching placebo. Results are anticipated by the end of 2016.

CONCLUSIONS

Prospective treatment studies to investigate the use of novel antivirals in rare conditions such as neonatal HSV, EV and CMV take many years to design, pilot and recruit. There are very few prospective cohort data describing the clinical features, laboratory markers and prognostic indices for neonates with severe viral infection. International pediatric clinical trial networks need to work together in partnership with the pharmaceutical industry to capture robust clinical and epidemiological observational data now to inform future treatment trial design. Due to the novel mode of action, it is hoped that both AIC316 and letermovir will be active against viruses that have developed resistance to current antiviral treatments. Both drugs are being prepared to enter phase 3 trials.

REFERENCES