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BCX4430 — A broad-spectrum antiviral adenosine nucleoside analog under development for the treatment of Ebola virus disease

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Summary The adenosine nucleoside analog BCX4430 is a direct-acting antiviral drug under investigation for the treatment of serious and life-threatening infections from highly pathogenic viruses, such as the Ebola virus. Cellular kinases phosphorylate BCX4430 to a triphosphate that mimics ATP; viral RNA polymerases incorporate the drug's monophosphate nucleotide into the growing RNA chain, causing premature chain termination. BCX4430 is active in vitro against many RNA viral pathogens, including the filoviruses and emerging infectious agents such as MERS-CoV and SARS-CoV. In vivo, BCX4430 is active after intramuscular, intraperitoneal, and oral administration in a variety of experimental infections. In nonclinical studies involving lethal infections with Ebola virus, Marburg virus, Rift Valley fever virus, and

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Yellow Fever virus, BCX4430 has demonstrated pronounced efficacy. In experiments conducted in several models, both a reduction in the viral load and an improvement in survival were found to be related to the dose of BCX4430. A Phase 1 clinical trial of intramuscular administration of BCX4430 in healthy subjects is currently ongoing.

Background

Nucleoside analog drugs have been highly successful in the treatment of a range of serious or life-threatening viral infections. Nucleoside analogs target fundamental reproductive mechanisms of the viral genome. For example, acyclovir, which was introduced in the 1980s to treat herpesvirus encephalitis [1,2], targets DNA polymerase; zidovudine, which was introduced in the 1990s to treat infections of human immunodeficiency virus [3], targets reverse transcriptase; and sofosbuvir, which was recently approved for the treatment of hepatitis C, targets RNA polymerase [4].

A viral-encoded RNA polymerase is essential for replication of RNA viruses in host cells and catalyzes the synthesis of multiple copies of complementary RNA from the template viral RNA. Each base-paired nucleotide is incorporated through specific binding of the triphosphate nucleotide to the enzyme and the RNA template, followed by cleavage of the pyrophosphate and covalent bonding of the 5′-monophosphate nucleotide to the 3′ position in the growing RNA strand. Therefore, desirable characteristics for antiviral nucleosides include efficient uptake into cells and efficient conversion of the nucleoside to the triphosphate nucleotide by mammalian kinases.

In fresh hepatocytes from mice, rats, non-human primates and humans in vitro (Fig. 1, left panel) and after an IM injection in rats in vivo (Fig. 1, right panel), BCX4430 is efficiently taken up into cells and converted to BCX4430 triphosphate (TP) [5]. In vivo conversion of BCX4430 to its TP nucleotide is particularly efficient; for example, the intracellular BCX4430-TP levels are higher than plasma levels of the parent compound within 30 min of intramuscular administration and continue to exceed the plasma drug levels by 10- to 100-fold for at least 24 h after a single dose.

As the molecular goal of antiviral therapy with RNA polymerase inhibitors is to interrupt viral RNA synthesis, a further desirable characteristic of a candidate nucleoside drug is structural mimicry of the corresponding natural nucleotide. This mimicry allows the drug nucleotide triphosphate to be recognized by the viral RNA polymerase and to be substituted for the corresponding natural nucleotide. Artificial nucleotides that are similar to either a natural purine (adenosine and guanosine) or a natural pyrimidine (uracil or cytosine) nucleoside may have structural modifications to either the base or ribose sugar moieties or both. BCX4430 (Fig. 2) is an adenosine analog, with substitution of carbon for nitrogen at position 7 on the base and nitrogen for oxygen at position 1 on the ribose ring.

Steric and electrostatic interactions and substitutions on the ribose ring are known to alter the conformation of the sugar. These conformational changes can in turn affect nucleotide incorporation and chain extension by polymerases. A structural change from a furanose in adenosine to an azasugar ring in BCX4430 alters the electrostatic interaction of the ring, and the viral RNA-dependent RNA polymerase is unable to add more than one or two further nucleotides, as demonstrated in vitro using a hepatitis C RNA polymerase assay (Fig. 3) [5].

In studies of ^{3}H-BCX4430 and ^{3}H-adenosine, the HuH-7 human hepatocellular carcinoma cell line was incapable of incorporating labeled BCX4430 into either RNA or DNA, despite avid incorporation of the labeled natural nucleoside [5]. The specificity of BCX4430 inhibitory activity, and likely that of other antiviral nucleoside drugs, for the viral RNA polymerase compared to the mammalian RNA and DNA polymerases is possibly due to the superior error—correction capabilities of the mammalian enzymes; however, other factors cannot be excluded.

Antiviral effect of BCX4430 in cell culture

Virus proliferation in cell culture is inhibited by incubation with BCX4430. BCX4430 displays a broad spectrum of activity against a wide variety of RNA viral pathogens. Many of these viruses, including MERS-CoV, EBOV, MARV, and YFV, cause serious