PRECLINICAL CHARACTERISATION OF MIV-802, A NOVEL URIDINE NUCLEOTIDE HCV NS5B POLYMERASE INHIBITOR, FOR TREATMENT OF HEPATITIS C VIRUS INFECTION

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BACKGROUND

HCV NS5B polymerase nucleotide inhibitors are considered as a central part of current and future interferon-free combination therapies for treatment of hepatitis C virus infection. The compounds have high pan-genotype activity and a high barrier to resistance making them highly attractive as part of shortened and simplified HCV treatment regimens.

OBJECTIVES

MIV-802 is a prodrug of a novel uridine analogue that is being advanced towards clinical development. The compounds have high pan-genotype activity and a high barrier to resistance making them highly attractive as part of shortened and simplified HCV treatment regimens.

MATERIALS & METHODS

• Antiviral activity for MIV-802 was evaluated using HCV replicons expressing NS5B sequences from HCV genotypes 1-6, including variants conferring resistance to nucleotides, and cellular isolates (from genotypes 1-4; Monogram Biosciences). 1,2
• The uridine nucleoside triphosphate (MIV-802-UTP) was tested for activity against purified HCV NS5B polymerase, and human induced pluripotent stem cells (iPS). Compounds were evaluated in a 7 day toxicology study at oral doses of 500 µM for up to 14 days.
• In collaboration with Claes Gustafsson (University of Gothenburg), the potential for MIV-802 to be incorporated into RNA by mitochondrial RNA polymerase (POLMRT), and the formation of full-length RNA product by 50% (Table 1).
• The mechanism of action for MIV-802-UTP was revealed to be inhibition of NC5B-catalyzed RNA polymerization through chain termination. The IC50 was 2.63 µM for MIV-802-UTP and 2.10 µM for sofosbuvir-UTP (Figure 1).
• MIV-802 displayed pan-genotypic potency in HCV replicons GTs 1-6 with an EC50 range of 17-58 nM (EC50 range for sofosbuvir: 48-210 nM) (Table 2).
• The antiviral profile of MIV-802 on a series of clinical isolates was also studied. For each GT, EC50 values obtained using MIV-802 were lower than those obtained using sofosbuvir, e.g. MIV-802 was 2.2-fold more potent than sofosbuvir against the GT1a panel (Figure 2).
• MIV-802 was evaluated for inhibition of HCV replicons encoding sofosbuvir-associated resistance substitutions in NS5B. The data revealed that, like sofosbuvir, 5282T confers low-level resistance to MIV-802, while L159F/L202F confers a small change in susceptibility (Table 3).
• MIV-802 did not affect erythroid proliferation but inhibited myeloid proliferation at 100 µM (47% inh, 14 days) which was similar to sofosbuvir (45% inh, 14 days). MIV-802-Nuc did not affect bone marrow progenitors at any concentration tested (IC50 >100 µM).
• MIV-802 had mild effects (40% inh) on cardiomyocyte function when incubated at the 100 µM for 14 days but had no effect at 50 µM. The effects were similar to sofosbuvir (22% inh). MIV-802-Nuc did not affect cardiomyocyte function. For comparison, clear inhibitory effects could be seen for INX-189 at 80 nM.
• MIV-802 and MIV-802-Nuc did not affect the viability of human primary cells such as dermal fibroblasts, renal proximal tubuli, hHUEC and hUMSC (IC50 >100 µM).
• No specific effects on mtDNA were detected when incubating HepG2 or HuH7 cells with MIV-802 and MIV-802-Nuc at up to 100 µM for up to 14 days.

CONCLUSIONS

• MIV-802 is a potent, pan-genotypic and selective nucleotide analogue with favorable resistance profile.
• MIV-802 displays high potency against replicons encoding NS5B sequences derived from HCV-infected patients with improved antiviral activity relative to sofosbuvir.
• MIV-802 shows good safety margins in vitro and in vivo and delivers pharmaceutically relevant amounts of UTP to human hepatocytes, and to dog liver after oral administration.
• Given its favorable preclinical profile, MIV-802 is currently being advanced towards clinical development.

REFERENCES