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Abstract (poster session)

No resistance detected to PMOplus antisense oligomers that protect nonhuman primates against marburgvirus

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Objectives: Marburgvirus (MARV) is highly virulent RNA virus of the family Filoviridae and a causative agent of viral hemorrhagic fever (VHF). The postexposure therapeutic efficacy of AVI-6003 [a PMOplus combination targeting MARV nucleoprotein (NP, AVI-7287) and VP24 (AVI-7288)] has reproducibly provided for 100 percent survival in nonhuman primate (NHP) MARV lethal challenge infections. The objective was to evaluate the viral sequence fidelity in viral genome regions targeted by AVI-6003 in nonhuman primates infected with MARV Musoke in treated versus untreated groups. Methods: Three independent studies were conducted in which cynomolgus macaques were infected with 1000 pfu of MARV Musoke. Five groups of infected NHPs included daily doses of AVI-6003, AVI-7287 alone, AVI-7288 alone, a negative-control PMOplus agent, and saline. Viral genomic RNA was obtained from infected animals immediately upon sample collection by mixing one volume of serum with three volumes of Triazol LS. Samples with > 300 pfu/mL were amplified using random hexamer DNA primers and reverse transcriptase PCR amplification. Viral genome sequence was determined using dye-terminator (studies 1 and 2) and pyrosequencing (study 3) methods. Results: The amplicon DNA sequence was determined to an average depth of up to 3300 for the NP site and 6700 for the VP24 site including an approximate 200 base flanking region. Determination of the entire viral genome sequence is currently in progress. The sequence observations encompass 3 independent studies, evaluating blood or serum samples from 35 different NHPs (29 treated at doses from 7.5 to 40 mg/kg/day and 6 saline controls), and samples were evaluated from days 8 to 30 post infection. The PMO targeted viral genome sites were found to demonstrate high fidelity and show no sequence changes indicating no development of resistanceto AVI-6003. Conclusions: These results indicate viral resistance to AVI-6003 and its components is unlikely in the genome of this single-stranded RNA human pathogen and support the further development of PMOplus therapies for use in humans.