Objective: Rabies is an ancient disease and until now no effective treatment is available. Treatment using short-interfering RNA (siRNA) to inhibit rabies virus (RABV) replication showed promising results in vitro. Our purpose was to evaluate the efficacy of siRNA in treating mice experimentally infected with different street RABV strains. Materials and Methods: 3 groups of 20 C57/BL6 mice, SPF, 4-6 weeks-old were inoculated in gastrocnemius muscle with 3 different RABV strains. A variant 2 isolated from a dog [d2v (LD50 10-3.39/0.03 mL)], a variant 2 isolated from a human [hv2 (LD50 10-6.66/0.03 mL)] and a variant 3 isolated from a human [hv3 (LD50 10-6.66/0.03 mL)] . For each group, 10 mice remained untreated and 10 mice were treated with a mix of 3 different siRNA sequences (3.3 μM each) associated with lipofectamine (Brandão et al. 2007) based on rabies virus N gene as a target. Animals received a single dose of siRNA mixture, via intraperitoneal route, 24h post RABV inoculation (p.i) and were observed during 30 days. Cox Proportional Hazards models were used to estimate lethality rates and Hazard Ratios (HR) between groups.

Results: For d2v, lethality was 37.5% in the inoculated group and 50% in the siRNA group (P= 0.71; HR= 0.75). For hv2, lethality was 100% in the inoculated group and 70% in the treated group (P= 0.27; HR=0.57). For hv3, lethality was 66% in the inoculated group and 80% in the treated group (P= 0.25; HR= 1.97).

Conclusion: The efficacy of siRNA seems to be associated to the RABV strain once the results of survival was variable in the groups submitted to siRNA and infected with different RABV strain. The siRNAs were used were designed based on Pasteur virus N gene sequence, a fixed strain while in our study street RABV strains were used. Even considered as a conserved gene, studies showed significant genetic variability. A nearly perfect complementary sequence between siRNA molecule and the viral RNA target is necessary for mRNA cleavage. Our RABV N gene sequences showed 85.7% - 92.2% of homology between v3 and siRNAs sequences and 95.2% – 100% to v2, confirming this natural variability and the better results obtained with the variant 2. In this study, a nonbiological delivery system was used and an important point is the difficulty of siRNAs delivery within CNS being this a major problem in practical therapeutic.

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