

论著

增殖诱导配体-siRNA/类脂质体复合体的临床前安全性评价

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摘要 目的 考察增殖诱导配体(APRIL)-小干扰RNA(siRNA)/类脂质体复合物的毒性。方法 1 小鼠iv给予APRIL-siRNA/类脂质体复合物500 mg·kg⁻¹,连续14 d称量小鼠体质量及观察死亡情况;2 每只豚鼠分别于第0, 7和14天左侧涂抹0.2 ml APRIL-siRNA/类脂质体复合物130 g·L⁻¹, 2, 4-二硝基氯代苯10 g·L⁻¹(阳性对照), 末次接触后14 d, 将各受试物0.2 ml涂于右侧, 持续6 h, 观察24和48 h皮肤致敏情况;3 小鼠分别iv给予APRIL-siRNA/类脂质体复合物125, 250和500 mg·kg⁻¹、环磷酰胺40 mg·kg⁻¹(阳性对照)组。间隔24 h, 第2次注射后6 h处死小鼠, 检测小鼠骨髓嗜多染红细胞微核率;4 小鼠分别iv给予APRIL-siRNA/类脂质体复合物125, 250和500 mg·kg⁻¹、环磷酰胺(阳性对照), 每天1次, 连续5 d, 检测小鼠精子畸形率。结果 与正常对照组相比, APRIL-siRNA/类脂质体复合物500 mg·kg⁻¹组小鼠体质量和各组织无明显变化, 没有小鼠死亡, 未表现急性中毒现象。APRIL-siRNA/类脂质体复合物对豚鼠皮肤无致敏性。该脂质体复合物125, 250和500 mg·kg⁻¹组小鼠骨髓嗜多染红细胞微核率分别为(1.8±1.0)%, (1.6±0.9)%和(2.4±1.1)%; 精子畸形率分别为(1.98±0.27)%, (1.96±0.15)%和(2.04±0.16)%, 与对照组微核率(2.2±1.3)%和精子畸形率(1.96±0.29)%无明显差异。结论 在本实验剂量范围内, APRIL-siRNA/类脂质体复合物对小鼠无明显毒性。

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Preclinical safety evaluation of APRIL-siRNA/lipoid plastid complex

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Abstract

OBJECTIVE To explore the APRIL-siRNA/lipoid plastid compound toxicity. **METHODS** 1 Mice were iv given APRIL-siRNA/lipoid plastid complex 500 mg·kg⁻¹ and body mass and death were observed for 14 d. 2 Each guinea pig was respectively given APRIL-siRNA/lipoid plastid complex 0.2 ml, 2,4-nitrochlorinated benzene 10 g·L⁻¹ or distilled water before administration on the left, at the seventh day and at the fourteenth day. After the last contact with 14 d, each guinea pig was given respective drug 0.2 ml on the right for 6 h. At 24 h and 48 h after the last administration, their skin reaction was observed. 3 Mice were iv given APRIL-siRNA/lipoid plastid complex 125, 250 and 500 mg·kg⁻¹, and cyclophosphamide 40 mg·kg⁻¹(positive control). Interval 24 h later, they were iv injected second time, and micronucleus rate test was detected after 6 h. 4 Mice were iv given APRIL-siRNA/lipoid plastid complex 125, 250 and 500 mg·kg⁻¹, and cyclophosphamide 40 mg·kg⁻¹ for 5 d, and sperm deformity rate was detected. **RESULTS** Compared with normal control group, body mass and organs of mice in APRIL-siRNA/lipoid plastid complexes group had no significance change, and no mice died. Compared with normal control(0%) group, sensitization rate in guinea pig skin in APRIL-siRNA/lipoid plastid complex groups (0%) had no significant change. Compared with normal control group, micronucleus rate in male mice in APRIL-siRNA/lipoid plastid complex 125, 250 and 500 mg·kg⁻¹ groups had no significant change [(2.2±1.1)% vs (1.8±1.0)%, (1.6±0.9)% and (2.4±

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1.3)%], sperm abnormal rate in APRIL-siRNA/lipoid plastid complex 125, 250 and 500 mg • kg⁻¹