NONCLINICAL SAFETY OF ALX-009, AN ANTIMICROBIAL THERAPY FOR CYSTIC FIBROSIS LUNG INFECTIONS

INTRODUCTION

The physical enhancement of microorganisms in the body may produce diseases transmitted by diverse mechanisms or mechanisms. In general, the microbial flora that colonizes the mucosa is normally considered innocuous, but may become pathogenic in certain circumstances. In the respiratory system, the colonization or invasion of infection agents leads to locally necrotic and specific infections that may cause local or widespread systemic involvement with subsequent sequelae.

In the lung, one of these defenses is the so-called mucociliary system. This system produces, among others, the hydrophobic (OSCN) with potent broad antimicrobial properties. OSCN is a highly reactive molecule that contains chlorine that destroys bacteria with certain antimicrobial and anti-inflammatory properties. Formation of free radicals by the introduction of OSCN to the respiratory system may cause damage to the lungs. This mechanism is used by the respiratory system to attack infective agents. The reaction of the OSCN with chlorine radicals generates singlet oxygen, which is involved in the destruction of pathogens.

TEST ITEMS

Although OSCN and its derivatives are naturally or acquired multidrug resistant bacteria such as Achromobacter, a multiresistant pathogen in the respiratory system, it is not affected by these molecules.

STUDY DESIGNS

The studies were performed in C57BL/6 mice, BALB/c mice, and BALB/c nu/nu mice. OSCN 10 mg/kg was administered as an oral treatment, i.e., i.p. and i.v. treatment, and by inhalation. Similarly, ALX-009 was administered as an oral treatment, i.e., i.p. and i.v. treatment, and by inhalation. The dosing duration was reduced for all groups to 28 days.

RESULTS AND DISCUSSION

GENOTOXICITY AND SAFETY PHARMACOLOGY FINDINGS (Table 1):

Under the experimental conditions of the study, ALX-009 did not show any genotoxic potential in any of the in vitro and in vivo tests performed. The analysis of autoradiography of the mouse lung demonstrated that OSCN and its derivatives are not affected by any of the tested molecules. OSCN is a highly reactive molecule that contains chlorine that destroys bacteria with certain antimicrobial properties. Formation of free radicals by the introduction of OSCN to the respiratory system may cause damage to the lungs. This mechanism is used by the respiratory system to attack infective agents. The reaction of the OSCN with chlorine radicals generates singlet oxygen, which is involved in the destruction of pathogens.

The toxicity profile of ALX-009 is described in Table 2. The most relevant findings related to the respiratory system, in rats, was the observed increase in respiratory distress observed after the administration of ALX-009. The respiratory distress was observed in 10% of animals administered with ALX-009. However, no signs of respiratory distress were observed in the control group. These findings were consistent with the observed reduction in body weight gain in some animals of the high dose group. The respiratory distress was observed after the administration of ALX-009 and was characterized by increased ventilation, increased respiratory rate, and increased respiratory depth. These findings were consistent with the observed reduction in body weight gain in some animals of the high dose group.

The analysis of undesirable pharmacological activity demonstrated that single or repeated dosing of ALX-009 in rats do not affect their behavior or physiological function as measured by a modified Irwin test. The analysis of undesirable pharmacological activity demonstrated that single or repeated dosing of ALX-009 in rats do not affect their behavior or physiological function as measured by a modified Irwin test.

CONCLUSIONS

- The safety pharmacology, genotoxicity as well as sub-acute and chronic administration toxicology testing demonstrated that ALX-009 does not induce major safety signals. In dogs, and during chronic administration, ALX-009 induced irregular breathing, coughing and gasping in some animals at the higher dose tested. However, these events were reversible and disappeared either after some off-dose periods or after dose reduction.

- bLF was occasionally detected in plasma, indicative of low risk of systemic exposure. Administration dose-dependent but non-linear bLF systemic exposure was observed in both species.

- Taken together, all results demonstrate that ALX-009 exhibits a favorable safety profile to support administration by inhalation to healthy volunteers and cystic fibrosis patients.