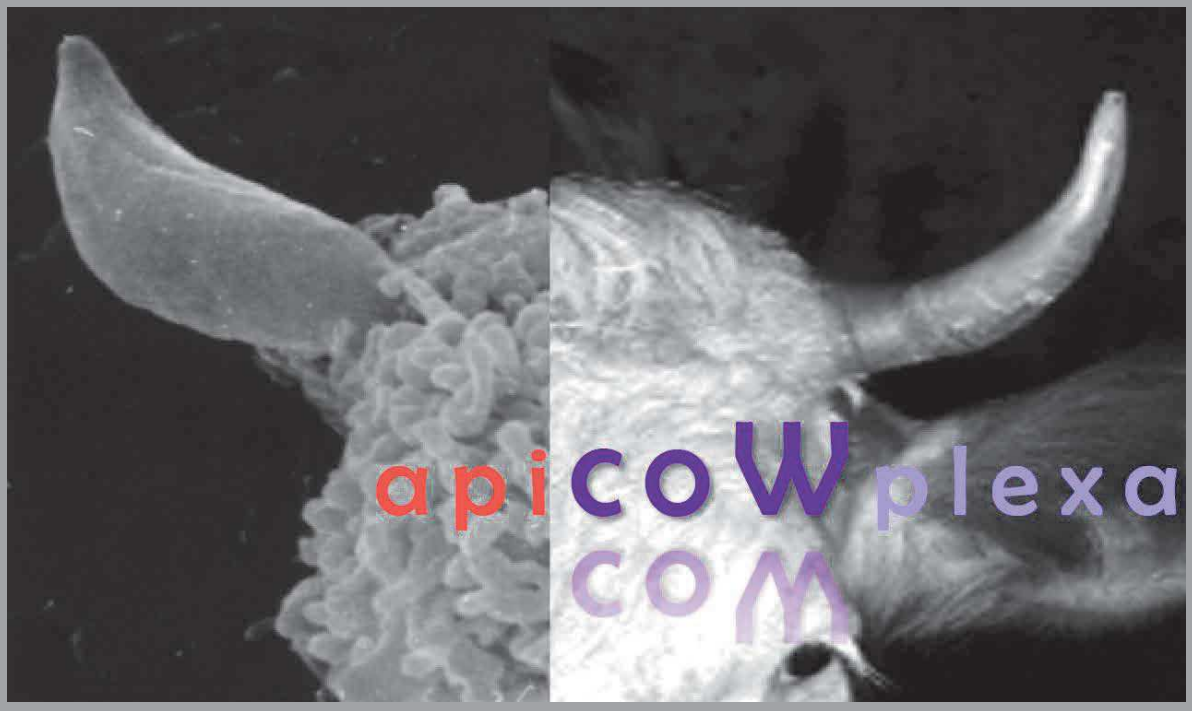
APICOWPLEXA 2017

4th International Meeting on Apicomplexa in Farm Animals, 11-14 October 2017 - Madrid, Spain



UNIVERSIDAD COMPLUTENSE MADRID

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Euroforum, El Escorial (Madrid, Spain)

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Pharmacokinetics, safety and efficacy of Bumped Kinase Inhibitor (BKI) 1553 in a pregnant sheep model of neosporosis

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Neosporosis is considered a major infectious cause of bovine abortion worldwide and despite the economic importance, at present there is no approved treatment for cattle. It has been demonstrated that calcium dependent protein kinases (CDPKs) are promising drug targets by compounds from a focused bumped kinase inhibitor (BKI) library. BKI-1553 *in vitro* acted with IC_{50} of 0.18µM and in a pregnant mouse model of neosporosis reduced vertical transmission of *N. caninum* to pups and increased the rate of survival of offspring. The aim of this work was to investigate the pharmacokinetics, safety and efficacy of BKI-1553 compound in a pregnant sheep model of neosporosis. Thirty seven pregnant ewes were allocated to 6 groups. Group 1 (G1) (n=8), group 3 (G3) (n=8) and group 5 (G5) (n=8) were intravenously (iv) inoculated with 10^6 tachyzoites of the Nc-Spain7 isolate at day 90 of gestation. Group 2 (G2) (n=5), group 4 (G4) (n=5), and group 6 (G6) (n=3) were iv inoculated with PBS. Beginning 48 hours after infection, BKI-1553 was administered subcutaneously to G1 and G2: 1st dose 35 mg/kg and 2nd dose 10 mg/kg a week later, and G3 and G4: 10 mg/kg, 7 doses every 48 hours. Pharmacokinetics was evaluated in plasma by liquid chromatography-mass spectrometry. Safety was assessed by rectal temperature, local reaction in the inoculation points, hematological and biopathological parameters, fetal viability and weight of the lambs. Efficacy was assessed by fetal mortality, humoral and cellular immune responses, histopathology and parasite detection and load in target tissues. Fetal mortality was observed in G1 (5 out of 8 pregnant ewes), G3 (4 out of 8 pregnant ewes) and G5 in all inoculated animals. Parasite detection was found in 100% placentomes/cotyledons in all infected groups. Regarding fetal tissues, significant higher detection percentage in brain was observed in G5 compared to G1 ($P < 0.05$) and G3 ($P < 0.05$). Furthermore, brain parasite burden in G5 was significantly ($P < 0.01$) higher than in G3. In conclusion, BKI-1553 seems to allow partial protection against abortion and decrease detection and parasite load in target fetal tissues in a pregnant ruminant model of neosporosis.

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