**DOXYCYCLINE EFFICACY IN A SURGICAL MODEL OF OSTEOARTHRITIS IN THE GUINEA PIG**

+*Glasson, S (E-Osteoarthritis Sciences, Inc.); **Harlan, P (E-Osteoarthritis Sciences, Inc.); ***Jimenez, P (E-Osteoarthritis Sciences, Inc); ****Haimes, H (E-Osteoarthritis Sciences, Inc)

+Genetics Institute/Wyeth, Cambridge MA. 617-665-5344, Fax: 617-665-5390, sglasson@genetics.com

INTRODUCTION

Doxycycline is reported to inhibit the expression and activity of MMPs, in particular collagenase-1 (MMP-1) and -3 (MMP–13). Collagenases are considered to have a major role in the progression of osteoarthritis. Beneficial effects of oral doxycycline have been reported in an accelerated dog model1 and a spontaneous guinea pig model2 of osteoarthritis (OA). In another report3, no effect of oral doxycycline was observed when administered for up to 8 months in the guinea pig spontaneous model. In this study, we evaluated the efficacy of oral and intra-articular doxycycline in our surgically induced model of OA in the guinea pig. The guinea pig was investigated as it does express MMP-1, in contrast to rats and mice4. Clinical trials are ongoing with doxycycline and in future, this MMP inhibitor may be the benchmark with which new classes of inhibitors are compared.

METHODS

Male Dunkin Hartley guinea pigs were used in an IACUC approved protocol. The oral doxycycline experiment used 18 (n=6 per group) five week old guinea pigs while the IA experiment used 37 (n=9-10 per group) eight week old animals. Anterior cruciate ligament transection and partial medial meniscectomy were performed through a medial arthrotomy with a #15 blade. The joint capsule was sutured with 5-0 Vicryl and the skin closed with wound clips. Oral Doxycycline (Vibramycin® Calcium syrup, Pfizer) at 3 and 15 mg/kg/day divided into twice daily treatments commenced on the day following surgery and continued for 9 weeks. Intra-articular (IA) doxycycline hydrochloride (Sigma) was prepared in a 2 mg/ml carboxymethylcellulose and 0.5 mg/ml polysorbate 80 vehicle to achieve final concentrations of 6 and 30 mg/ml. The particle size was measured using a Coulter Multisizer Accucomp. Doxycycline injections were commenced at 2 weeks post-operatively and consisted of 50μl (0.3 and 1.5 mg) per week injected through the patellar tendon of the flexed knee into the patellofemoral joint. A group of 10 animals were sacrificed at 2 weeks for the IA doxycycline study to evaluate the efficacy of oral and IA doxycycline groups directly compared.

RESULTS

Animals receiving oral doxycycline calcium had normal weight gain and exhibited no diarrhea throughout the study. No reduction in Mankin score was observed in the 3 or 15 mg/kg oral doxycycline group when compared to the no treatment group (Figure 1). The doxycycline hydrochloride had a mean particle size of 1.0μm and no side effects were observed with weekly IA injection. Both the 0.3 and 1.5 mg/week IA doxycycline groups had statistically reduced (p<0.05, unpaired t-test) Mankin scores (Figure 2). The 1.5 mg/week group had higher weights than for the no treatment group (data not shown).

DISCUSSION

Intra-articular doxycycline dramatically retarded OA progression, as measured by Mankin score, in a surgically-induced model of OA in the guinea pig. When doxycycline was administered IA, the Mankin scores at 9 weeks approximated those seen at 2 weeks post-operatively and reflected no disease progression once prophylactic doxycycline was initiated. We did not observe oral efficacy which may be related to a low doxycycline dosage, inadequate bioavailability in the guinea pig, the immature collagen network present in 5 week old guinea pigs or that the severity of OA in this model is too great for oral doxycycline therapy to overcome. Based upon reported antimicrobial doses of Doxycycline (5-20 mg/kg/day) and a report indicating that 20mg/kg for 5 days/week for 12-18 months decreased OA progression in a spontaneous OA model in guinea pigs, we believe we had a sufficient dosage and bioavailability in our model. A subsequent guinea pig study observed no benefit of oral doxycycline when administered for 4-8 months1. This experiment should be repeated however, with animals of the same age and oral and IA doxycycline groups directly compared.

The dosages for which IA doxycycline efficacy was seen was at a 225 fold lower dose than that of the inefficacious oral dose. This suggests that IA therapy may be advantageous when drug supply is limiting or where side effects may be an issue. The dramatic benefits of IA administration in this study support the use of doxycycline as an agent to inhibit the progression of OA in the clinic.

REFERENCES


ACKNOWLEDGEMENTS

Thanks to Gene Mercado, Felicitas Eldred, Jeffrey Lauer, Anthony Chavarria and Burkhart Kriwet for technical assistance.

**MIT, Cambridge, MA .
 ***Novartis, NJ.
 ****Bioheart, Framingham, MA.

48th Annual Meeting of the Orthopaedic Research Society
Poster No: 0685