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Prevention of Barrett's Esophagus (BE) and Esophageal Adenocarcinoma (EAC) in the Levrat rat model of EAC by treatment with the smoothened (SMO) inhibitor

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Background: EAC from BE is increasing and the prognosis is poor. The Hedgehog (Shh) pathway may play a role in BE/EAC. The Levrat model of gastroduodenojejunal reflux mimics progression from normal to EAC. We studied the activity of a SMO inhibitor (BMS 833293) for prevention of BE/EAC.

Methods: Reflux was induced in 6-8 wk old male Sprague–Dawley rats as previously described (approved by the animal IRB). At ten weeks post-op, rats were divided into treated and control groups. Based on PK and information provided by BMS, a PO dose of 10mg/kg/day was used. Drug was given daily, weeks 10-16, 18-22 and 24-28. One pathologist (JD) evaluated all samples. IHC for proliferation and apoptosis (Ki67 and caspase 3) was scored. In treated animals that developed tumors, drug target gene expression was analyzed. All tumor specimen data was compared to non-operated, control rat esophageal epithelium.

Results: Survived to 28 wks/operated: control (38/48); treated (32/46). Animals with wt loss >20% were removed. Specimens from 38 control and 32 treated were evaluated by one pathologist (JD). Control: BE/noBE=35/3 and EAC/noEAC=22/16. Treatment: BE=19/13 ($p=0.0002$) and EAC=7/25 ($p=0.0033$). Gene expression for Ihh was 184X higher in BE and 99X in EAC. ($p<0.05$). Per IHC, Ki67 was decreased in tx ($p=.04$), and caspase 3 cleavage was upregulated in tx ($p=0.398$). Analysis of 84 genes potentially related to resistance revealed 28 dysregulated genes ($p<0.05$).

Conclusions: Levrat model is feasible, and there was a significant prevention effect for BE and EAC. Proliferation was downregulated, and differential regulation of pathway genes suggests mechanisms for drug escape.

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