Withdrawal of sirolimus prior to wound injury does not compromise healing

Luke A. Umana[1], Nikolaos, M. Nikolaidis[1], Jason C. Gardner[1], John G. Noel, Lori B. Pitstick, Kenneth D. Setchell and Francis X. McCormack
[1]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati College of Medicine Cincinnati, OH
[2]Division of Pathology and Laboratory Medicine, Cincinnati Children's Hospital Medical Center

Background
Impaired wound healing is a complication of sirolimus use. Sirolimus stabilizes lung function in lymphangioleiomyomatosis (LAM) patients, but sirolimus is contraindicated in those listed for transplant due to reports of late bronchial anastomotic dehiscence. These events occurred in patients who received the drug continuously after transplant, however not in patients who took the drug preoperatively and discontinued it when the call for transplant came.

Aims/Hypothesis
To determine the wound healing capacity of rodents 1-2 weeks after sirolimus is withdrawn.

Methods
To assess pharmacokinetic activity of sirolimus in our mouse model, Hsd:NSA (CF-1) mice were given 1 mg/kg/day sirolimus intraperitoneal injections for four days. Serum levels were measured at 1, 24 and 72 hours after the last sirolimus dose. Lungs were formalin fixed and the conducting airway epithelial cells were stained for ribosomal ps6. To determine if sirolimus clearance was sufficient to alter wound healing *in vivo*, mice were given 1 mg/kg sirolimus or vehicle for 4 days and bilateral full thickness wounds were made on the dorsal aspect of the animals. Change in dimensions due to wound healing was measured at days 7 and day 14. Wound biopsies were collected and analyzed for hydroxyproline content and angiogenesis with anti-PECAM1 (CD31) antibody.

Results
Sirolimus displayed bimodal elimination with a half-life of 5.18 hours in the first 24 hours, followed by 11.56 hours from 24-72 hours. Sirolimus levels were below limit of detection (<1 ng/mL) at 72 hours. Sirolimus suppressed constitutive phosphorylated ribosomal s6 in conducting airway epithelium, and sirolimus elimination restored baseline ps6. Mice treated with interrupted sirolimus displayed similar wound healing when compared to the vehicle control. Continuously sirolimus treated animals displayed significant wound healing impairment. In addition, continuously treated animals displayed significantly decreased degree of vascularity assessed with anti-CD31 antibody compared to the vehicle and interrupted group.

Conclusions
When sirolimus treatment is interrupted on the day of wounding, long-term wound healing is unimpaired. These data challenge the practice of withdrawing sirolimus in listed LAM patients and should facilitate discussion of allowing them to continue the drug until the transplant day arrives.

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