

Evaluation of Imatinib Mesylate as a Possible Treatment for Nephrogenic Systemic Fibrosis in a Rat Model

Thomas A. Hope¹, Philip LeBoit², Whitney A. High³, Yanjun Fu¹, and Robert C. Brasch⁴

¹Radiology and Biomedical Imaging, UCSF, San Francisco, CA, United States, ²Dermatology, UCSF, San Francisco, CA, ³Dermatology, University of Colorado, Denver, CO, ⁴Radiology, UCSF, San Francisco, CA

One promising treatment for NSF is imatinib mesylate (Gleevec; Novartis). The first report of treating NSF with imatinib came out in 2008, and showed improvement of lesions while on imatinib and that the lesions worsened when the imatinib was stopped. We decided to evaluate the efficacy of imatinib in the prevention of dermal changes in a rat model of NSF.

MATERIALS AND METHODS: The study design was based upon a previously published protocol. 24 rats were randomly separated into four groups of six animals. Group A was injected with normal saline as a control; group B, IV iron and Epo; group C, gadodiamide, IV iron and Epo; and group D, gadodiamide, IV iron, Epo and imatinib. Epo (epoetin alfa) was administered by SC injection at a dose of 100 u/kg 3 days per week for five weeks. IV iron (iron dextrose) was administered by IV injection at a dose of 4 mg/kg over five days. Groups C and D received gadodiamide (Omniscan, GE Healthcare) 10 mmol/kg by IV injection for five consecutive days. Group D received 50 mg/kg per day of imatinib mesylate. Skin biopsies were obtained after three and seven weeks. Histology was performed using with hematoxylin and eosin and CD34. Nuclei cell counts were performed in the superficial and deep dermis. Samples were also analyzed using ICP-MS to measure deposited gadolinium and iron.

RESULTS: The administration of high dose gadodiamide resulted in increased dermal fibroblast-like spindle cellularity in comparison to saline treated animals, which was seen both in the superficial and deep dermis (Figure 2 and 3 – superficial: group A = 80 cells/hpf versus C = 332, $p < 0.001$; deep: group A = 75 vs C = 243, $p < 0.001$). A large portion of these cells stained positive for CD34. Treatment with IV iron and Epo alone did not result in changes in dermal cellularity. The concomitant administration of imatinib (group D) resulted in decreased cellularity (superficial: group D = 194 cells/hpf, p -value for C vs D = < 0.001 ; deep: group D = 164, p -value for C vs D = 0.02). There was no significant difference in the amount of dermal gadolinium between group C and D. At 7 weeks dermal cellularity decreased in both the superficial and deep dermis.

DISCUSSION: The administration of imatinib to rats treated with high dose gadodiamide resulted in decreased lesion severity suggesting that imatinib may be effective in the treatment of NSF in humans.

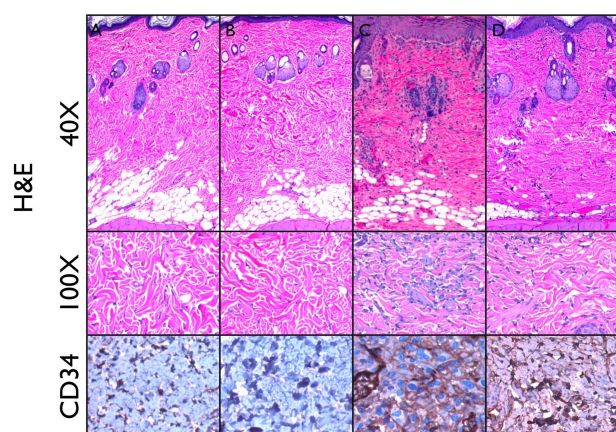


Figure 1: Representative H&E (rows 1 and 2) and CD34 stains (row 3) Increased dermal cellularity can be seen in groups C and D. With imatinib treatment (group D) there is decreased cellularity in comparison to gadodiamide alone (group C).

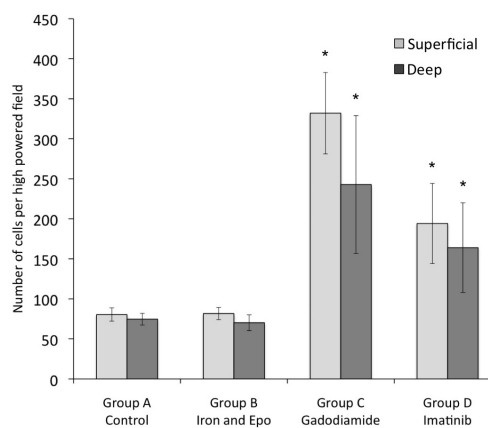


Figure 2: Nuclei cell counts in the dermis at three weeks, measured in the superficial and deep dermis. Treatment with gadodiamide resulted in a marked increase in both superficial and deep dermal cellularity. The coadministration of imatinib limited this increase in cellularity.

1. Kay J. 2008. 2. Hope TA. Radiology 2009; 253:390-398. 3. Sieber MA. Invest Radiol 2008; 43:65-75.