

Apr 12, 2022

Subject: Sirolimus/GFJ Study

To: mjr1@uchicago.edu

<https://pubmed.ncbi.nlm.nih.gov/22872575/>

This amazing study, trying to get some further insight.

1. In the adverse events table, how is that “apparently” Sirolimus/GFJ at several doses has fewer adverse events, including fewer DLT? How does such a large boost in Cmax/AUC not result in resoundly higher adverse/DLT thresholds?

2. Did you find a pattern between age and/or metabolic state and adverse events/DLT?

I started taking Rapamycin a year ago, and a few months, with GFJ for simple longevity...slowly trying to find some practical upper dose limit.

Thank you for your email. In regard to your questions, we reduced the dose in conjunction with grapefruit juice to avoid the risk of toxicity due to high exposure.

We did not have a sufficient sample size to look at predictors of adverse events, although increased glucose and triglycerides are indicators that the drug is working.

I will add that I have serious reservations about the use of sirolimus for general prophylactic purposes, since the drug can cause both serious interstitial lung disease, as well as anemia due to impaired iron utilization.

Best of luck,

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Thank you Mark.

Sorry for the layperson follow-up...the study was underpowered to elicit differential impact on adverse events between Sirolimus and Sirolimus/GFJ? You suggest that I should not lend credence to the insignificant delta in adverse/DLT between Sirolimus and Sirolimus/GFJ at the "same dose"?

Do you have references for your "reservations" advisement? Anemia was one of the adverse events in your study.

I donate blood every 8 weeks regularly, would be characterized as iron deficient, without anemia...12+ months on Rapamycin, no ill effects.

But this is a SERIOUS drug...carefully monitoring.

The gastrointestinal toxicity associated with the high weekly doses we were using is due to drug that was. It absorbed. This would potentially be reduced by grapefruit juice. But I have never used high dose weekly sirolimus outside of this study.

Sirolimus affects iron utilization, and I have encountered issues with apparent iron deficiency in my own practice with daily doses of 3-4 mg (without grapefruit juice).

Mark J. Ratain, M.D. (from my iPhone)