A Letter to the Editor Regarding the Original Article by Mulhall et al: Utility of Tacrolimus (FK506) trough level for the Prevention of Erectile Dysfunction

It was with great interest that we read the article by Mulhall et al., published in the Journal of Sexual Medicine, which is the first clinical trial that aimed to explore whether tacrolimus (FK506) can improve erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Previous animal research showed that FK506 exerted neuroprotective and neurotrophic effect, which can contribute to limiting cavernous neural damage and speeding up nerve recovery from injury. Although this trial was well designed and conducted, the authors failed to prove any potential benefits of improving erectile dysfunction after receiving FK506. However, we have noticed 1 flaw that the authors ignored: FK506 trough level monitoring was not conducted.

In this article, there was no statistical difference in IIEF-EFD score at 18–24 months between the FK506 and placebo arms. Furthermore, the study drug was reduced in 35.6% of patients in the FK506 group, compared with 20% in the placebo group (P = .07) because of adverse effects. It is generally known that the immunosuppression effect of FK506 is trough level dependent; the neuroprotective effect may act the same way. Hence, a possible explanation for the negative results is that not all patients reached an effective trough level at the same dose because of the different metabolism of FK506 in each individual. FK506 is metabolized by CYP 3A4 and 3A5, which has a great distribution variation in humans. This means that similar dosing may yield distinct results: underexposure may not show any protective benefits, whereas overexposure can lead to more adverse events. However, experiment animals are more homogeneous than humans, genetically and physically, and that same dosing results in similar trough levels, which may be the reason why the positive results cannot be replicated in humans.

For the trial by Mulhall, we recommend 2 additional comparisons of FK506 trough levels. For the first, compare FK506 trough levels between patients with and without functional recovery in the FK506 treatment arm, which determines the minimum trough level with curative effect. For the second, it should be conducted between patients with and without reduced FK506 simultaneously, which can help to determine the therapeutic window of target trough levels without significant adverse effects. Then, take patients achieving and maintaining the target therapeutic window of FK506 as a new arm, and compare their IIEF-EFD score with that of their counterparts in the control arm. A better way is to redesign a randomized control trial with FK506 trough level monitoring, making dose adjustments according to the target therapeutic window, to verify whether tacrolimus is helpful in erectile dysfunction recovery after patients undergo nerve-sparing RP.

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