

Dear Dr. Chesney

Dr. Shimazu let me know that the Pediatric Advisory Committee will discuss on potential cancer risk among pediatric patients treated for atopic dermatitis with topical dermatological immunosuppressants at on Monday, February 15, 2005.

I also would like to make some comment on this issue, as I have analyzed the carcinogenic animal experiment disclosed as the SBA that is available in Japan and I made some comment to the committee member before the final discussion of tacrolimus ointment for pediatric use(0.03%) at Japanese advisory committee on 26th June 2003.

I summarized the point that I wrote and send to the committee member before the final discussion of tacrolimus ointment for pediatric use(0.03%) at Japanese advisory committee on 26th June 2003.

I am also attached a ppt slides that is a brief summary of the above.

1. Immunosuppressant and cancer risk in post-transplantation patients (Slide 1)

Tacrolimus is an immunosuppressant. Suppressed immunity could cause infection and/or cancer.

In fact, post-transplantation risk of tacrolimus treatment inducing PTLD is reported 10~20% in 5 years follow-up for children(1-8) and 1~5% in 5 years for adults.

It may reasonably estimated up to 30-50% in children, if followed more than ten years, because the risk is much more higher in children than in adults (9) and the risk was reported up to 15% of patients treated with cyclosporine for 13 years(10). Moreover tacrolimus may be more potent than cyclosporine(8,11) .

The virus-infected mice treated with 2 mg/kg of tacrolimus for 30 days developed lymphomas and other hemoblastic disorders by nearly five-fold compared to untreated animals(12).

Malignancies induced by immunosuppressants are not only lymphoma but also cancer of all sites ([13,14,15](#))

Spectrum of toxicities of immunosuppressants are wide: for example fibrosis of myocardium is observed in the carcinogenicity animal experiment and cardiomyopathy is observed clinically, skin proliferation with inflammatory reaction (dermatitis) is observed in the the carcinogenicity animal experiment and

neurotoxicities and renal impairments were observed([16](#)).

2. Cancer risk of tacrolimus ointment treated mice (Slide 2)

Cancer risk of all sites of mice treated with 0.03% tacrolimus ointment was significantly greater than that of mice treated with vehicle ointment.

Comparison with “sham” is not appropriate according to the ICH guideline.

Risk of malignant lymphoma treated with 0.03% tacrolimus ointment was also significantly greater than that of mice treated with vehicle ointment.

Advisory committee on 26th June 2003, recommended the reexamination of carcinogenicity study because the existing carcinogenicity study was not conclusive.

3. Dose-risk curve of carcinogenicity experiment of tacrolimus ointment(Slide 3)

I calculated the excess cancer risk by sex and by tacrolimus ointment potency according to the following formula:

Excess risk=(risk of treated mice - risk of vehicle mice) / (1 - risk of vehicle mice)

I also calculated the tacrolimus plasma concentration by sex and by tacrolimus ointment potency from the AUC data.

And I plotted the data on concentration-excess cancer risk relationship on a graph. I simulated the dose-response (risk) relation. It is well fitted to the logistic curve.

4. Summary of tacrolimus risk (Slide 4)

1. Plasma concentration of tacrolimus for transplantation is 10~20 ng/mL: It is the same level as of the mice carcinogenic plasma level.
2. Maximum clinical blood level of tacrolimus treated as ointment is estimated about 2 ng/mL. It is only one third of the mice carcinogenic plasma level.
3. ICH guidance recommended that maximum clinical level should be 25 times less than the least carcinogenic level in the rodent based on AUC (or 150 times less than that mg/kg base).

4. So animal carcinogenicity test show that it's approval violates the ICH guidelines.
5. We have no experience using tacrolimus ointment in enough periods for inducing cancer. But if you carefully analyze the animal carcinogenicity study, you can predict it's cancer risk with significant extent.
6. Animal carcinogenic results are excellent warnings for the risk of long term topical use of immunosuppressant.

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