**Drug-Drug Interaction between Trastuzumab Emtansine (T-DM1) and Orally Administered Tacrolimus in a Patient and in Rat**

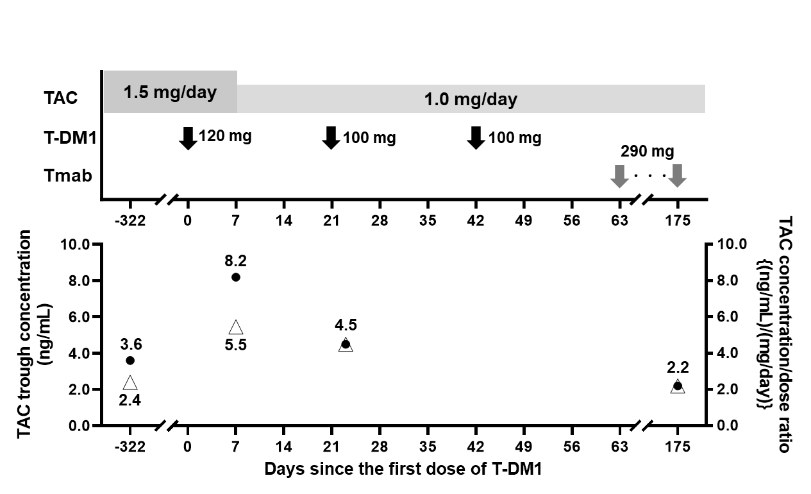
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**Background and aim.** Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) composed of trastuzumab (Tmab) and N2'-deacetyl-N2'-(3-mercapto-1-oxopropyl)-maytansine (DM1), a cytotoxic drug (payload). Compared to small molecule drugs, ADCs are considered less likely to interact with metabolic enzymes such as CYPs or drug transporters. However, we have experienced a 2.3-fold increase in the trough concentration of orally administered tacrolimus in a patient for 7 days after intravenous administration of T-DM1. The aim of this study was to confirm and clarify the mechanism of this drug-drug interaction using rat model.

**Methods.** We conducted a detailed retrospective clinical study of the interaction between T-DM1 and tacrolimus in this case and conducted animal experiments using rats to examine the putative pharmacokinetic interaction.

**Results.** Retrospective clinical study revealed no change in factors known to alter the pharmacokinetics of tacrolimus, and the change in the trough concentration of tacrolimus was reversed after switching T-DM1 to trastuzumab (Tmab). Thus, interaction with T-DM1 was suspected as the cause of the increased trough concentration of tacrolimus. An animal study in rats showed that T-DM1 significantly increased the AUC0-∞ of orally administered tacrolimus by more than 2-fold on day 0, day 3, and day 7, whereas no change was observed in the case of intravenous administration of tacrolimus. T-DM1 also significantly increased Fa・Fg of tacrolimus by more than 2-fold on day 7. In contrast, Tmab itself had no effect on the blood concentration of tacrolimus. These results suggest that T-DM1 increased the blood concentration of orally administered tacrolimus, and the effect persisted for 1 week after T-DM1 administration.



**Figure 1.** Clinically administered doses of tacrolimus (TAC), T-DM1 and trastuzumab (Tmab), trough concentration of tacrolimus (●), and concentration/dose (C/D) ratio of tacrolimus (△)

The patient was taking tacrolimus (1.5 mg/kg or 1.0 mg/kg) orally and then T-DM1 (120 mg or 100 mg) or Tmab (290 mg).

**Conclusion/Discussion.** An increase in the blood concentration of orally administered tacrolimus was observed after intravenous T-DM1 administration in a patient and the interaction was confirmed in an animal study. It is known that T-DM1 is metabolized and the metabolites predominantly undergo biliary excretion. It was suggested that metabolites of T-DM1, rather than Tmab itself, affected the gastrointestinal absorption of tacrolimus.

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