Examination of CYP3A5 gene polymorphisms was useful for adjusting doses of tacrolimus in outpatients with rheumatic diseases

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[Background] Tacrolimus (TAC) is widely-known as an immunosuppressive drug. In Japan, unlike foreign countries, it is also indicated for many autoimmune diseases such as myasthenia gravis, systemic lupus erythematosus, and rheumatoid arthritis. As TAC has a narrow range of effective blood concentration, it requires strict control of blood concentration with therapeutic drug monitoring (TDM). Because outpatient treatment involves examinations usually once per month, we cannot conduct confirm the concentration by TDM so much frequently as inpatients. This makes it difficult to adjust the TAC dosages, leading to delay of the treatment.

Moreover, various genetic polymorphisms are known to be involved in TAC metabolism. In kidney transplant patients, those with CYP3A5 gene *1/*1 or *1/*3 have stronger metabolic activity than those with *3/*3, and it has been reported that it is significantly more difficult to raise TAC blood concentration in such patients. Therefore, we measured CYP3A5 genetic polymorphisms in outpatients with rheumatic disease and investigated their relationship with TAC blood concentration and administration dosages.

[Methods] CYP3A5 6968A>G genetic polymorphisms were measured in 50 outpatients being treated with TAC at Shinko hospital. Patients, continuously taking TAC for at least two weeks and examined a clear blood concentration by TDM were divided into two groups: the *1/*1 + *1/*3 group and the *3/*3 group. Then, blood concentration/dosage ratio (C/D ratio) was compared.

[Results] Genetic polymorphisms for the patients were measured and divided into three groups: CYP3A5 *1/*1 group, *1/*3 group and *3/*3 group were 3 patients (6.3%), 19 patients (40.4%) and 25 patients (53.2%), respectively. In the 41 patients in which TAC blood concentration was clarified, the C/D ratio was compared in 18 patients in the *1/*1+*1/*3 group and in 23 patients in the *3/*3 group. The C/D ratio of CYP3A5 *1/*1+*1/*3 group was 1.41 ± 0.76 ng/ml/mg and significantly lower than 3.21 ± 2.37 ng/ml/mg that of CYP3A5 *3/*3 group, $P < 0.01$.

[Conclusions] The CYP3A5 gene diagnosis before TAC administration may enable the dose prediction of the patients and are an important information to support safer TAC therapy for our outpatients.