学 位 論 文 の 要 旨

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学 位 論 文 名　Long-lasting Renal Dysfunction Following Tacrolimus Induction Therapy in Ulcerative Colitis Patients

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論 文 内 容 の 要 旨

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by abdominal discomfort as well as such complications as rectal bleeding, abdominal pain, and body weight loss. Tacrolimus (TAC), one of the available calcineurin inhibitors, is an immunosuppressive drug that inhibits T lymphocyte activation and proliferation. Recently, TAC has been used as an alternative medication for steroid-dependent or -refractory patients with moderate to severe UC activity. Furthermore, oral TAC therapy for steroid-refractory UC has been shown highly effective for shortening the acute phase and rapidly inducing mucosal healing. As a result, guidelines used in several different regions of the world now recommend administration of TAC for steroid-dependent or -refractory UC. On the other hand, there are adverse events related to TAC treatment, with nephrotoxicity one of the most serious of those encountered in cases treated with the drug for various diseases, forcing some patients to discontinue use due to renal dysfunction. Previous studies have also shown that TAC can induce vasoconstriction of afferent arterioles that reduces glomerular blood flow, resulting in renal ischemia, which can finally lead to reversible renal failure. Unfortunately, this condition remains poorly understood in regard to UC cases, with only a few related reports presented. The present

retrospective study was conducted to determine the impact of oral TAC on renal function when given for remission induction therapy in UC patients.

MATERIALS AND METHODS

Fifty-five UC patients (10 elderly, 45 non-elderly) with moderate to severe activity and treated with oral TAC were enrolled. At the time of drug initiation, TAC was administered at a dose of 0.1 or 0.05 mg/kg/day, which was then adjusted to achieve a high target trough level of 10-15 ng/ml. Two weeks after starting treatment, the dosage was again adjusted to produce a low target trough level of 5-10 ng/ml. After 12 weeks of administration, TAC was withdrawn or continued depending on clinical response. All patients were evaluated using the Lichtiger index, as previously reported, with clinical remission defined as Lichtiger index ≤ 3. Renal function was assessed using estimated glomerular filtration rate (eGFR), calculated using the modification in renal disease (MDRD) equation. The rate of change in eGFR was defined as the ratio of eGFR at that time point as compared to the baseline (start of TAC administration). The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

As for disease extent, 45 (81.8%) of the 55 analyzed patients had extensive colitis and 10 (18.2%) left-sided colitis. Additionally, 15 (27.3%) were prednisolone (PSL) resistant and 33 (60.0%) were PSL dependent, while the other 7 (12.7%) were naïve to PSL. Thirty-seven (67.3%) achieved clinical remission (Lichtiger index ≤ 3) at week 12 and the median duration of TAC administration was 118 days (97-173). Furthermore, the median time from start of TAC treatment required to reach the target blood trough concentration (10-15 ng/ml) was six days (4-8.5), with a maximum trough level of 18.2 ng/ml (15.2-22.7) noted during treatment on day 19 (10.5-39.5). Overall, the median target trough concentration in blood at one, two, and 12 weeks after the start of TAC was 12.3 ng/ml (10.1-14.9), 10.2 ng/ml (8.0-13.2), and 8.1 ng/ml (6.8-10.1), respectively. A gradual reduction in eGFR rate was seen until the end of treatment with TAC, with the average change after one, two, four, and 12 weeks found to be -7%, -8.4%, -12.9%, and -20.3%, respectively, after starting administration. Nearly all of the patients had a significant decrease in eGFR as compared with their pre- and post-treatment TAC values. Improved eGFR was promptly observed after cessation of TAC (-8.9% at four weeks, -5.1% at 12 weeks after ending treatment), though none showed recovery to the baseline eGFR at either 52 or 104 weeks following termination (eGFR change: -9.2% and -11.2%, respectively). Multivariate linear regression analysis showed that the rate of change in eGFR at week 12 was significantly correlated with age ($\beta = -0.3242$, $p = 0.0103$) as well as maximum serum trough level during treatment ($\beta = 0.3563$, $p = 0.0051$). Of the 55 UC patients analyzed, 10 were elderly

and 45 were non-elderly. Eight (80%) in the elderly and 29 (64.4%) in the non-elderly group reached clinical remission within 12 weeks. On the other hand, there was no significant difference for median target trough concentration during the course of treatment between the groups [week two: 12.9 ng/ml (9.8-15.3) vs. 12.7 ng/ml (11.5-13.9), week 12: 8.1 ng/ml (7.0-10.2) vs. 6.9 ng/ml (5.8-8.4)]. Furthermore, five (50%) of the elderly patients showed progression from CKD stage G1 or G2 to G3a/b by the end of treatment, while 39 (86.7%) of those in the non-elderly group were in CKD stage G1 or G2 at the completion of TAC, and then 94.2% were found to be at the same stage two years later, with only 5.8% in CKD stage G3a/b.

This is the first known study to present results of long-term monitoring that show an association of TAC-induced renal dysfunction with patient age. First, while eGFR values were within normal limits before treatment in the present cohort, a declining trend was shown early after beginning TAC regardless of age and then continued throughout the administration period, with the lowest values as compared to the baseline noted at 11 weeks. Second, though not previously reported for other diseases, renal function in the present UC patients for up to two years after TAC discontinuation was analyzed. Those findings showed that eGFR improved quickly after cessation of TAC, though recovery to pre-treatment levels was not attained even after two years. These results indicate that TAC-induced nephrotoxicity may be sustained in patients with UC for a prolonged period after discontinuation of treatment. As for renal function, the rate of decline in eGFR was significantly greater in the elderly as compared to non-elderly patients from the first week of TAC administration until the end of treatment, whereas there was no difference in serum trough concentration during treatment between those groups. Furthermore, even after TAC was stopped, recovery of eGFR in the elderly was significantly worse as compared with the non-elderly patients. Elderly individuals generally have a lower metabolic capacity and significantly greater risk for developing kidney damage as compared to non-elderly, which may have influenced the present results. Nevertheless, our findings suggest that renal function should be carefully followed for a long period after completion of TAC therapy in elderly patients.

CONCLUSION

The present study provides evidence that oral TAC treatment given as remission induction therapy for moderate to severe UC has beneficial effects in both non-elderly and elderly patients. Notably, a TAC-induced decline in eGFR was observed in most cases, with that especially noted in the elderly group for an extended period after cessation. Therefore, careful monitoring of renal function is crucial to better elucidate the balance between the benefits and risks of TAC treatment. In addition, oral TAC should be cautiously administered to elderly patients and avoidance may be better because of effects on renal function.