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Optimal Pharmacokinetics of Cyclosporine and Tacrolimus Based Relationship Among AUC, Trough and Peak Concentration

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1. Introduction

Calcineurin inhibitors (CNIs) are maintenance immunosuppressive drugs that have been used as the main therapy for organ transplantation for many years. Of the CNIs, cyclosporine (CYA) and tacrolimus (TAC) are used in clinical practice. The CYA binding protein is cyclophilin and that of TAC is FK-binding protein (FKBP), but both drugs have same mechanism of action: the inhibition of interleukin 2 (IL-2) production by binding the binding protein complex to calcineurin (CN). It is thought that the area under the concentration time curve (AUC) for both drugs may be the pharmacokinetic (PK) parameter that is the most associated with clinical effect. However, oral CYA administration gave a blood concentration-time curve with a high CYA peak concentration (C_p), and oral TAC showed a gradual blood concentration-time curve, keeping at the minimum of the therapeutic range; both drugs vary significantly in their pharmacokinetics¹. The C_p of CYA has increased since the Neoral® preparation of CYA was used, compared with Sandimmune®, whereas the C_p of TAC decreased since using a sustained release preparation; thus the differences between CYA and TAC are considerable². Although the optimal pharmacokinetics of both drugs may be similar to those of other drugs with the same mechanism of action, no conclusions have been reached on whether the peak blood concentration, or a specific maintained blood concentration, is required for CNI pharmacokinetics, even if both drugs show identical AUCs. In addition, although CYA and TAC are similar CNI drugs, there are differences in the recommended monitoring points of CYA and TAC; these points are the C_2 level (the blood concentration 2 h after oral administration), which mainly reflects C_p , and the trough concentration (C_t)³⁻⁸, respectively⁹⁻¹¹. To solve these problems, it is necessary to consider comprehensively not only AUC, but also C_p , C_t , and time above the minimum effective concentration (%T > MEC). We discuss the optimal pharmacokinetics of CNIs by comparing various aspects of CYA and TAC.

2. Which parameter is the most closely associated with clinical results?

2.1 Cyclosporine

It is a well-known fact that C_t is associated with clinical effect. As when the C_t become higher, the AUC and the C_t are consequently higher. it is not surprising that C_t , C_p , and

AUC are all correlated with clinical effect. The question, therefore, is which of these PK parameters is the most associated with clinical effect. It is commonly thought that the AUC of CYA is most closely associated with clinical effect^{12,13}). However, it is often difficult to measure AUC₀₋₁₂ for 12 h after administration in clinical practice. Accordingly AUC₀₋₄ (the area under the concentration time curve at 0–4 h following oral administration) is generally used as an alternative absorption phase to AUC₀₋₁₂. This earlier blood sampling point that has been used since the introduction of cyclosporine microemulsion concentrate (Neoral), in which oral absorption is significantly stabilized^{3,14}). Even AUC₀₋₄ requires several blood sampling points, and this causes problems such as increased burden on patients, cost, and medical staff duties. It has therefore been recommended that a single blood sampling point, C_2 , be used; this is the sampling point at which the majority of patients show peak level in the absorption phase, and is better correlated with AUC₀₋₁₂ than C_0 ³⁻⁸). It has been reported that AUC₀₋₄ and C_2 are associated with the incidence rate of acute rejection and nephropathy or similar conditions^{3,15-19}), and a relationship with clinical effects and side effects was demonstrated. Nevertheless, there are several problems relating to the use of C_2 because its determination involves the measurement of absorption values. As it means the change in blood concentration over time is great; there is a possibility that C_2 may vary significantly over a small interval in blood sampling times, in comparison with trough value^{20,21}), and complicated procedures for outpatients are increased. Given the above, the monitoring of C_2 in routine clinical practice is questionable^{22,23}), and it has been reported that there is little evidence in which it is useful to monitor C_2 ²⁴).

2.2 Tacrolimus

On the other hand, the AUC of TAC, like that of CYA, is commonly considered to be a parameter which is highly associated with clinical effect, despite little evidence for TAC treatment showing clinical effects such as acute rejection^{25,26}) or side effects such as nephrotoxicity²⁷). Therefore, TAC was examined to show which blood sampling point is the best correlated with AUC as CYA. One study reported that C_0 is the best correlated with AUC²⁷), whereas another study suggested that a formula with fewer blood sampling points, and not C_0 , is the most closely correlated with AUC (limited sampling strategy)²⁸⁻³¹).

Thus, although the AUC of CNIs is regarded as the PK parameter, which is the most closely associated with clinical effect, its monitoring point is not clear. In addition, it has not been much discussed whether the peak blood concentration, or a specific maintained blood concentration, is required for pharmacokinetics even if both drugs show identical AUC. For the purpose of solving this problem, the authors analyzed the pharmacokinetics of CYA and TAC by comparing AUC, C_p , and C_t parameters, used not as independent parameters but in a new manner, which could indicate the interrelationship between these parameters.

2.3 Comparison between pharmacokinetics of oral cyclosporine and tacrolimus¹⁾

There has been no study comparing the differences between the blood concentration time curves of CYA and TAC in detail. Therefore, the authors thought that the pharmacokinetics of both drugs could be compared by using the blood concentration ($C/D/BW$), adjusted for dose per body weight. Although the AUC/(D/BW) of both CYA and TAC, which should show the relative availabilities, was equal, the $C_p/(D/BW)$ of CYA was comparatively higher than that of TAC and, on the other hand, the $C_t/(D/BW)$ of CYA was lower than that

of TAC, which illustrated a blood concentration time curve with a sharp peak. On the other hand, the pharmacokinetics of TAC showed that the $C_p/(D/BW)$ of TAC was lower and the $C_t/(D/BW)$ was higher, which illustrated a gently hunched blood concentration time curve, which was similar to the curve for continuous intravenous infusion (Figure 1, Table 1).

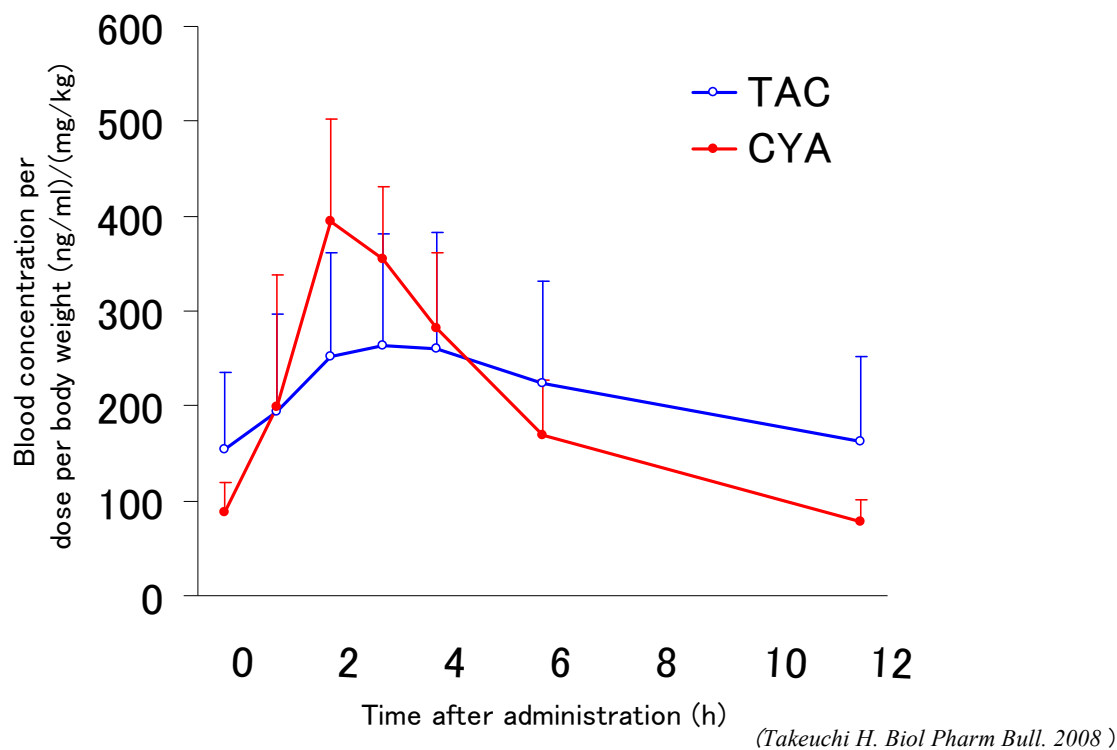


Fig. 1. Comparison of the mean blood concentration-time curves for CYA (n=20) and TAC (n=24)

| | CYA (n = 20) | TAC (n = 24) | p value |
|---|-----------------|-----------------|---------|
| AUC/D/BW _{(ng/mL·h)/(mg/kg)} | 2323±447 | 2507±1255 | N.S. |
| C _p /C _t | 6.00±1.78 | 1.93±0.43 | <0.0001 |
| C _p /D/BW _{(ng/mL)/(mg/kg)} | 433.1±90.3 | 292.6±135.7 | <0.005 |
| C _t /D/BW _{(ng/mL)/(mg/kg)} | 77.1±23.6 | 160.0±91.8 | <0.005 |
| AUTL/AUC (%) | 41.9±6.9 | 73.4±8.1 | <0.0001 |

(Takeuchi H. Biol Pharm Bull. 2008)

Table 1. Comparison of pharmacokinetic parameters between CYA and TAC

Thus, even if the AUC of both drugs were equal, the pharmacokinetics of the both drugs is totally different, from the viewpoint of the correlation with each peak value and each trough value. We developed AUTL/AUC% (percentage of the area under the trough level in the

area under the blood concentration) in order to assess the interrelationship between AUC, C_p , and C_t in comparing CYA and TAC (Figure 2). As a result, the AUTL/AUC% of CYA was as low as 41.9%, and the AUC had a higher percentage of dependence on C_p than on C_t . On the contrary, the AUTL/AUC% of TAC was as high as 73.4%, and the AUC had a higher percentage of dependence on C_t than on C_p (Figure 3).

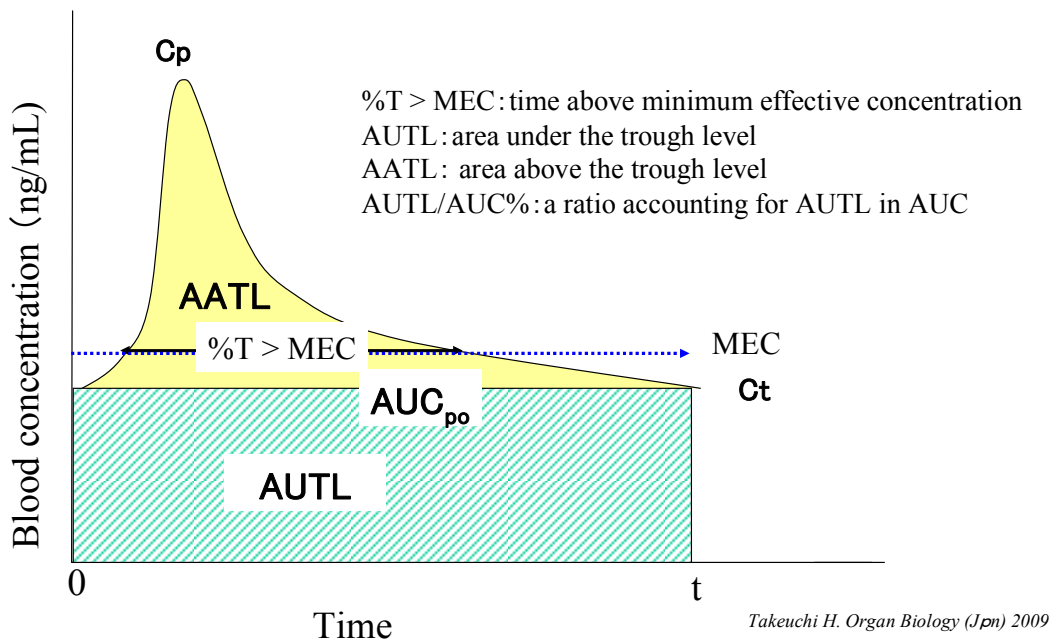


Fig. 2. Blood concentration curve and pharmacokinetic parameters

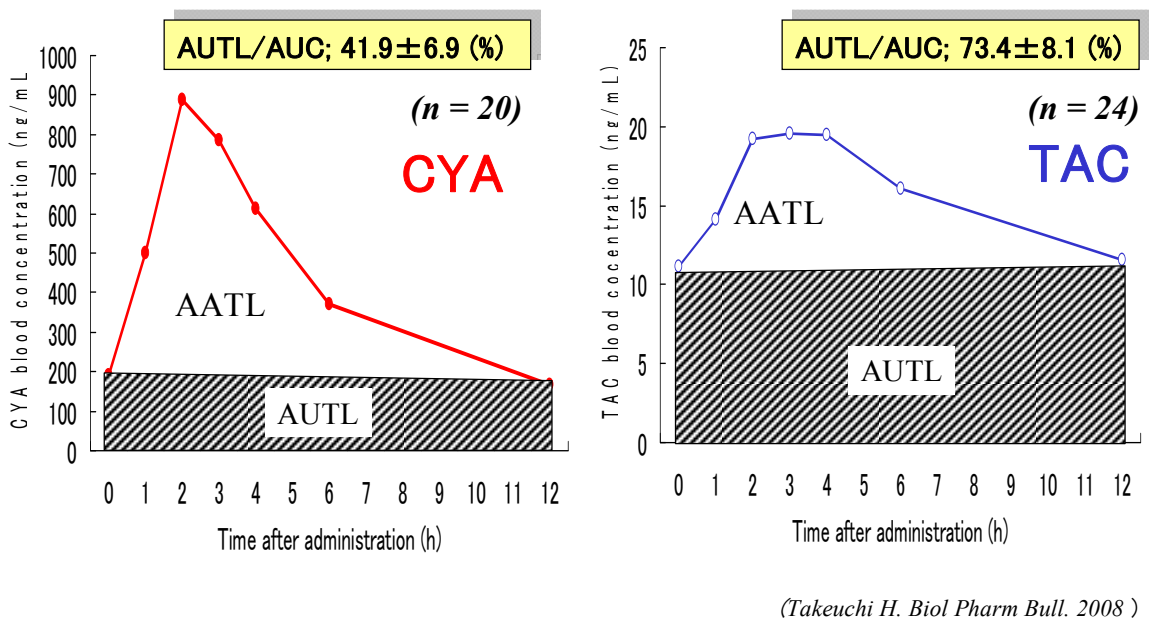


Fig. 3. Comparison of the pharmacokinetic parameters of AUTL/AUC% between CYA and TAC.

To demonstrate these results further, we examined the correlation between the AUC and the area above trough level (AATL) or AUTL, and found that these results were consistent with

the theory that CYA had higher correlation with AATL, and TAC had higher correlation with AUTL (Table 2). If AUC is most closely associated with clinical effect, it may be appropriate to monitor C_p and C_t for CYA and TAC, respectively. However, considering that the blood concentration per unit time for C_p changes dramatically, and taking into account the measurement convenience and complexity of the methods, it is thought that TAC to measure C_t is preferable as a drug to perform TDM than CYA to recommend measuring C_2 . However, it is thought that C_t as monitoring point is not a clinical problem, as the measurement of CYA C_t reflects the AUC adequately.

| | correlation coefficients (R^2) | |
|--------------|------------------------------------|--------------|
| | AUC vs. AUTL | AUC vs. AATL |
| CYA (n = 20) | 0.7110 | 0.9024 |
| TAC (n = 24) | 0.9029 | 0.7123 |

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Table 2. Comparison of correlation coefficients between AUC and AUTL or AATL in CYA- and TAC-treated recipients

Furthermore, the influences on clinical effect, such as effectiveness or side effects, would be different between pharmacokinetics with a higher peak value, namely with low AUTL/AUC% and pharmacokinetics with a maintained minimum effective concentration, namely with high AUTL/AUC%, such as the blood concentration of continuous intravenous infusion, even if the AUC of both drugs were equal. By illustrating this, as shown in Figure 4, it is possible to see a difference between the pharmacokinetics of A and B, even if both AUCs are equal. The C_{max} of A is lower than that of B but the C_{min} of A is higher than that of B. This relation can be applied to the correlation of CYA and TAC discussed above. In addition, considering PK parameters involved pharmacodynamics (PD) such as the minimum effective concentration (MEC), A may maintain MEC over a certain time ($\%T > MEC$), which is longer than for B, even if the AUCs for both A and B are equal. CNIs may be a drug for which time above MIC (MEC) is associated with drug efficacy, as is the case with antimicrobial agents such as beta-lactam antibiotics, This suggests that the effects of A and B may be different, by the correlation of AUC, C_p , and C_t .

Thus, the examination of clinical effect using only AUC is limited, and therefore, an analysis including the interrelationship between AUC, C_p , C_t , and time is required.

3. Correlations among AUTL/AUC%, effects, side effects, and PK parameters for other drugs practicing TDM

Table 3 shows the results of correlations among the PK parameters, effects, and side effects of current drugs investigated for TDM in the literature. As a result, the blood concentration time curves can be classified into the following categories: a drug group showing a sharp peak curve (AUTL/AUC < 50%, $C_p/C_t > 6$), such as aminoglycoside antibiotics (AGs), and a drug group showing a gentle peak curve (AUTL/AUC% > 60%, $C_{max}/C_{min} < 2$), such as antiarrhythmic drugs, bronchodilators, and anticonvulsant drugs (Figure 5).

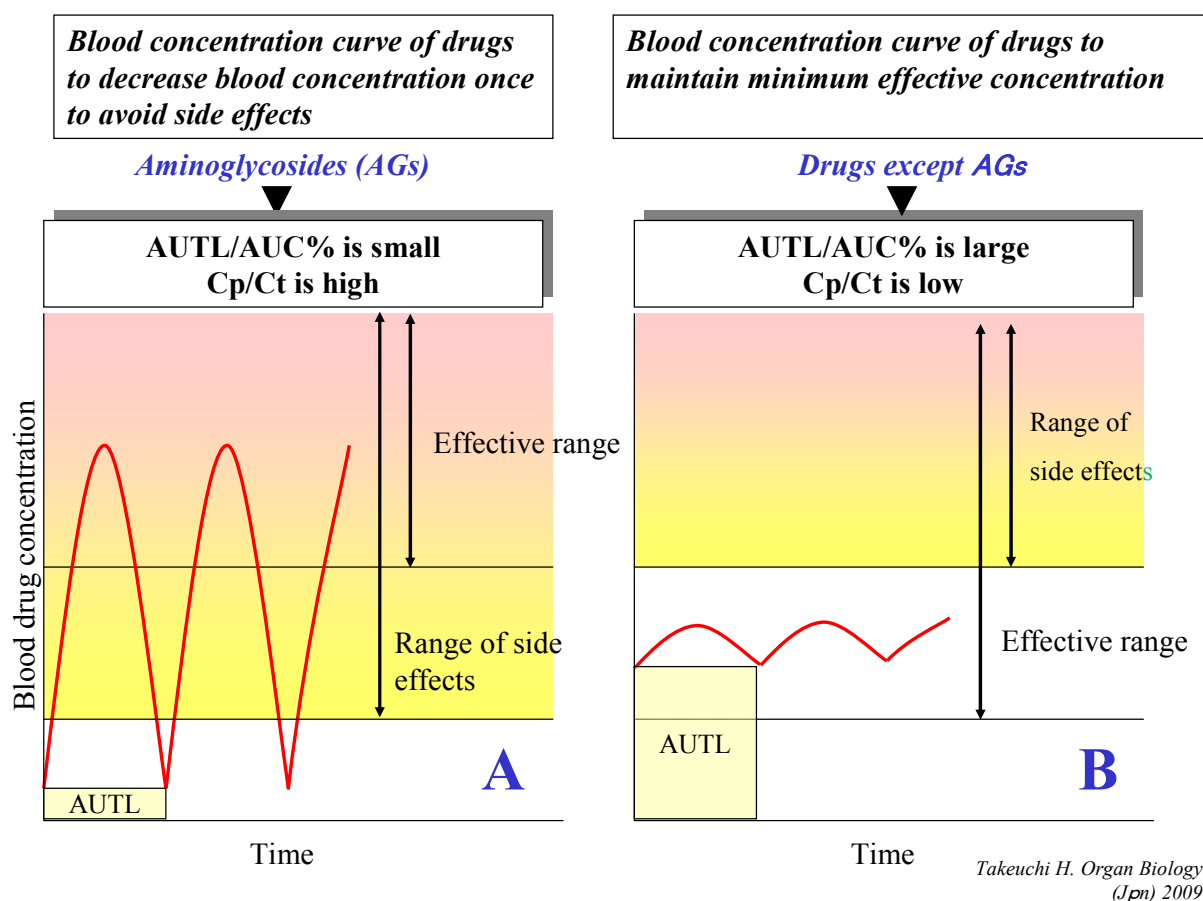


Fig. 5. Two patterns of blood concentration curve based on AUTL/AUC%

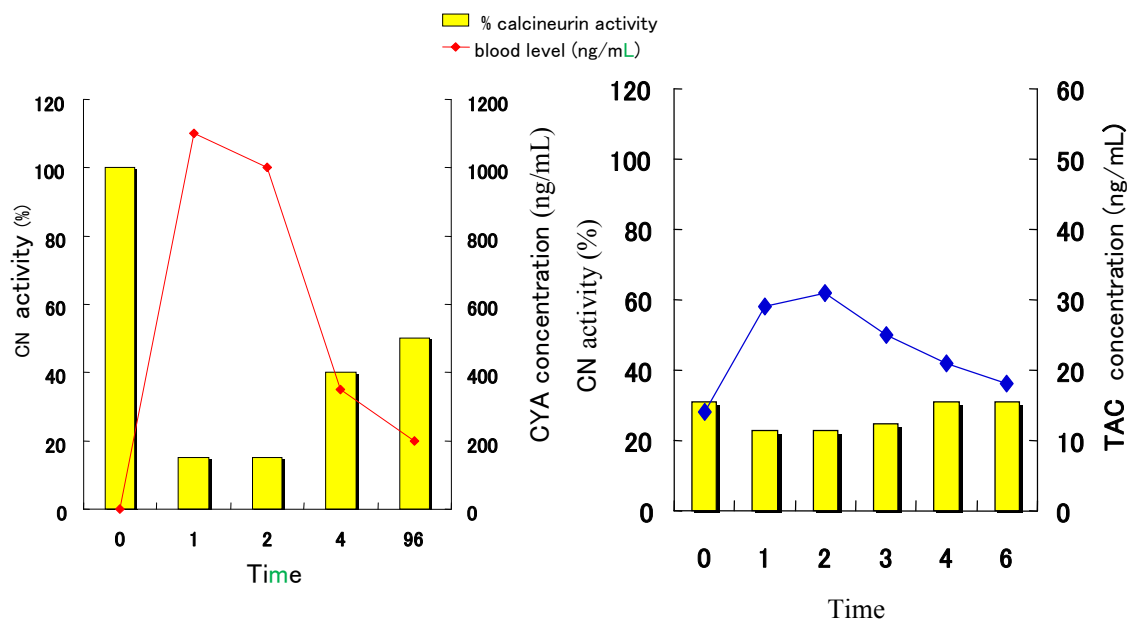
All drugs except AGs, glycopeptide antibiotics, and CYA, which required $\text{AUTL/AUC}\% \geq 60\%$ and $\text{C}_p/\text{C}_t \leq 2$ to maintain the therapeutic range, had a gentle blood concentration time curve and the monitoring point was C_t . It is preferred that AGs maintain a concentration to the peak value for as long as possible, but it must be reduced to below a specific blood concentration on a temporary basis to avoid nephrotoxic side effects. Therefore, $\text{AUTL/AUC}\%$ decreased to a low level and C_p/C_t increased to a high level to show a blood concentration time curve with a sharp peak. Furthermore, AGs have a post-antibiotic effect (PAE), so that it can maintain its effect even if it falls below the therapeutic range.

Furthermore, the pharmacokinetics of AGs and glycopeptide antibiotics relate to administration by injection, and these drugs are not required to control a clinical condition for a long period. Therefore, the results showed that CYA (Neoral) was the only oral drug used for prevention of a long-term pathologic condition that showed a sharp peak curve. Drugs with a sharp peak concentration were the only drugs for which the blood concentration needed to be reduced on a temporary basis to avoid side effects, and there was no drug that needed to be at peak concentration in order to have an effect. However, when the CYA used was switched from Sandimmune to Neoral to increase and stabilize absorption, the absorption rate constant (K_a) became large such that the peak value necessarily increased, and the $\text{AUTL/AUC}\%$ decreased.

CYA may not require higher peak concentration, if the trough concentration can be higher to keep the AUC, although it is impossible that raising the trough value and decreasing the peak value (to increase the AUTL/AUC%) using the existing CYA formulation, keep the AUC.

4. Optimal pharmacokinetics based on PK/PD analysis

In connection with the preceding paragraph, regarding patients treated with CYA (Neoral), it has been reported that the inhibitory action of CN was in proportion to the blood concentration following administration³²⁾, and that IL-2 was stably suppressed at the peak value rather than the trough value³³⁾. On the other hand, another report showed that TAC above a certain level continuously had an inhibitory action of CN after administration³⁴⁾. It is possible that the differences between the both drugs may contribute to these results (Figure 6). In other words, CYA shows sufficient CN inhibitory action at the peak value, but the data suggests that the CN inhibitory action may be insufficient at the trough value. On the other hand, TAC is at a concentration that shows a certain level of CN inhibitory action throughout all time points, including the trough value, which suggests that it may always show inhibitory action of CN above a certain concentration.



Halloran P, Focus on Medicine, No. 13, 1998

Pernille B et al., Transplant 2001: Abstract #1076,
Takeuchi H. Organ Biology (Jpn) 2009

Fig. 6. Relationship between blood concentration and calcineurin activity in CYA and TAC.

The authors analyzed the relationship of the concentration–lymphocyte proliferation rate curves (PD) of CYA and TAC with the target blood concentration (PK) and found that lymphocyte proliferation was completely suppressed at the trough level of TAC. On the other hand, CYA had a low inhibition ratio at the trough value and was more than sufficient inhibited at the peak value, so that there was no need for the concentration to be as high as the peak value in terms of pharmacodynamics; consequently, it was necessary to make the trough value higher (Figure 7).

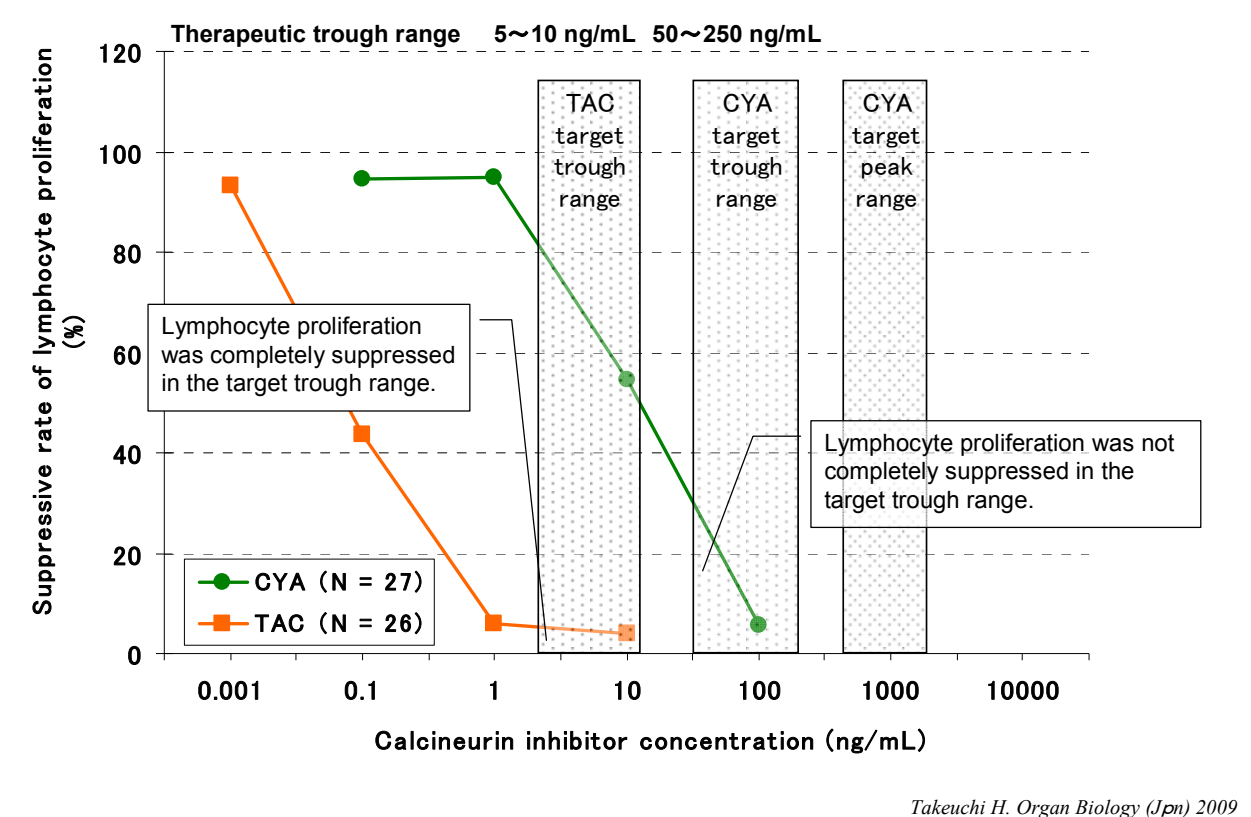


Fig. 7. Relationship between average concentration-lumphocyte proliferation rate curves and target blood concentration of calcineurin inhibitors.

5. Optimal blood concentration for continuous intravenous infusion based on AUC

Currently, intermittent intravenous administration and 24-h continuous intravenous administration can be compared for optimal pharmacokinetics in clinical practice.

For patients undergoing hematopoietic stem cell transplantation, drugs are administered by intravenous injection for relatively long periods, from several weeks to several months, because ingestion is not possible. However, the theoretical optimum targeted blood concentration for continuous infusion has never been clearly determined. If AUC is the parameter most closely associated with clinical effect, it can be considered correct, in theory, to adjust the blood concentration of oral and intravenous administration to the level that achieves the same AUC. We used the AUTL (area under trough level) parameter developed by the authors to calculate the target blood concentration for continuous intravenous infusion from the trough level for oral administration^{35,36}. As a result, the target blood concentration for continuous intravenous infusion of TAC (C_{ss}) was 1.4 times that of the C_t because AUTL/AUC% is large. These results were almost close to the blood concentration in the present practice of continuous intravenous infusion. Meanwhile, CYA has a small AUTL/AUC% so that a trough value 2.55 times higher and a considerably high C_{ss} were required in theory (Figure 8).

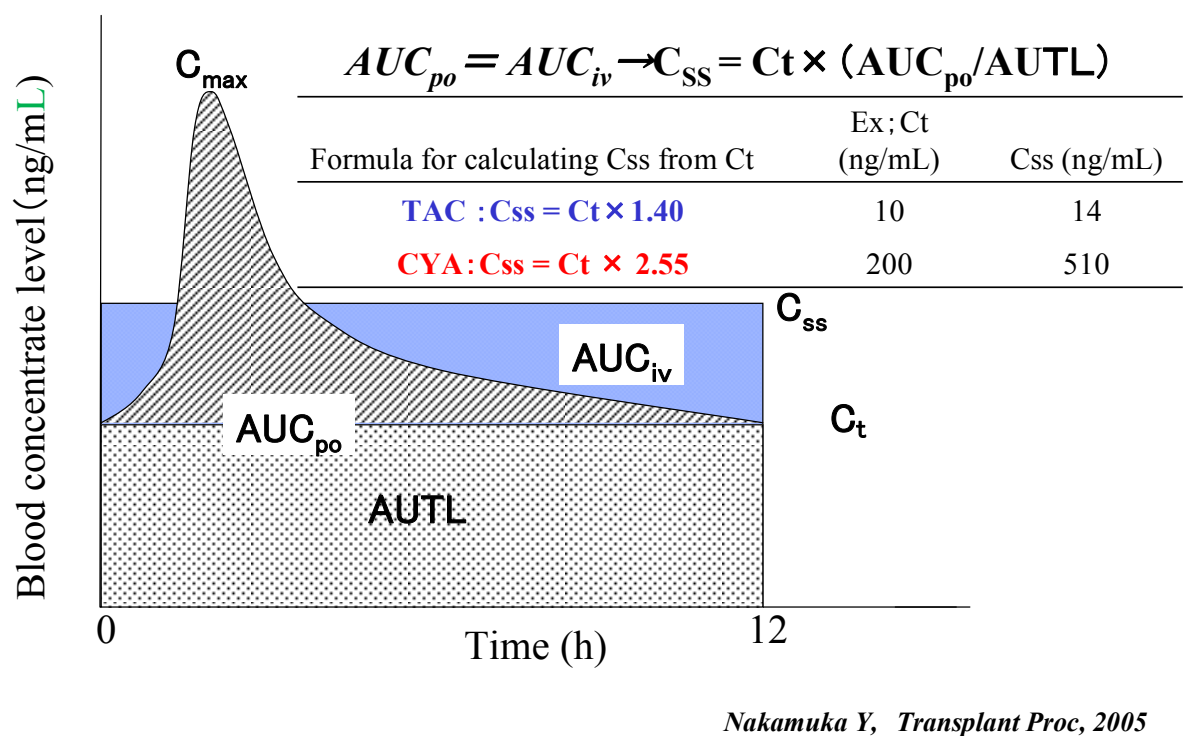


Fig. 8. Formula for calculating C_{ss} from C_t, and the relationship between the AUC of oral administration and continuous intravenous infusion.

In actual hematopoietic stem cell transplantation, it has been reported that continuous intravenous infusion of CYA at 250–400 ng/mL C_{ss}, which is lower than the theoretical value, showed lower nephrotoxicity than intermittent intravenous administration twice a day, and that the incidence rate of acute graft-versus-host disease (GVHD) was high³⁷. However, in a study by the same group, comparing a 300 ng/mL C_{ss} group with a 500 ng/mL C_{ss} group, it was reported that the incidence rates of acute and chronic GVHD were significantly lower in the 500 ng/mL group, and there was no difference in side effects, such as nephrotoxicity, between both groups of the trial³⁸. In another study by Miller et al. using a C_{ss} of 450–500 ng/mL, similar results on acute GVHD and tolerability were reported³⁹ and these reports were consistent with the authors’ hypothesis. Continuous intravenous infusion is the ultimate method for maintaining a minimum effective concentration (Figure 4-A), and it may be possible for the pharmacokinetics to have no peak if the AUC of CYA can be obtained; in other words, the pharmacokinetics as minimum effective concentration is maintained.

Meanwhile, in many institutions, patients undergoing hematopoietic stem cell transplantation received different dosages, such as 3 mg/kg/day twice a day (3 h continuous infusion) by I.V. infusion, once a day (4 h continuous infusion) by I.V. infusion, once a day (10 h continuous infusion) by I.V. infusion, and 24 h continuous intravenous. However, there are slight differences in the clinical results⁴⁰. Each AUC was

almost the same, at around 11,000 ng·h/mL, in all the dosages above, but the results calculated by the authors revealed that each AUTL/AUC% was approximately equal (35–44%) in intermittent administration and it was 100% in continuous intravenous infusion (Figure 9). Moreover, we set various therapeutic ranges to simulate and calculate %T > MEC and found that the values significantly varied depending on MEC (Figure 10). These results suggest that CYA has a wide tolerance of blood concentration in terms of action and side effects, and that all dosages might be clinically equal.

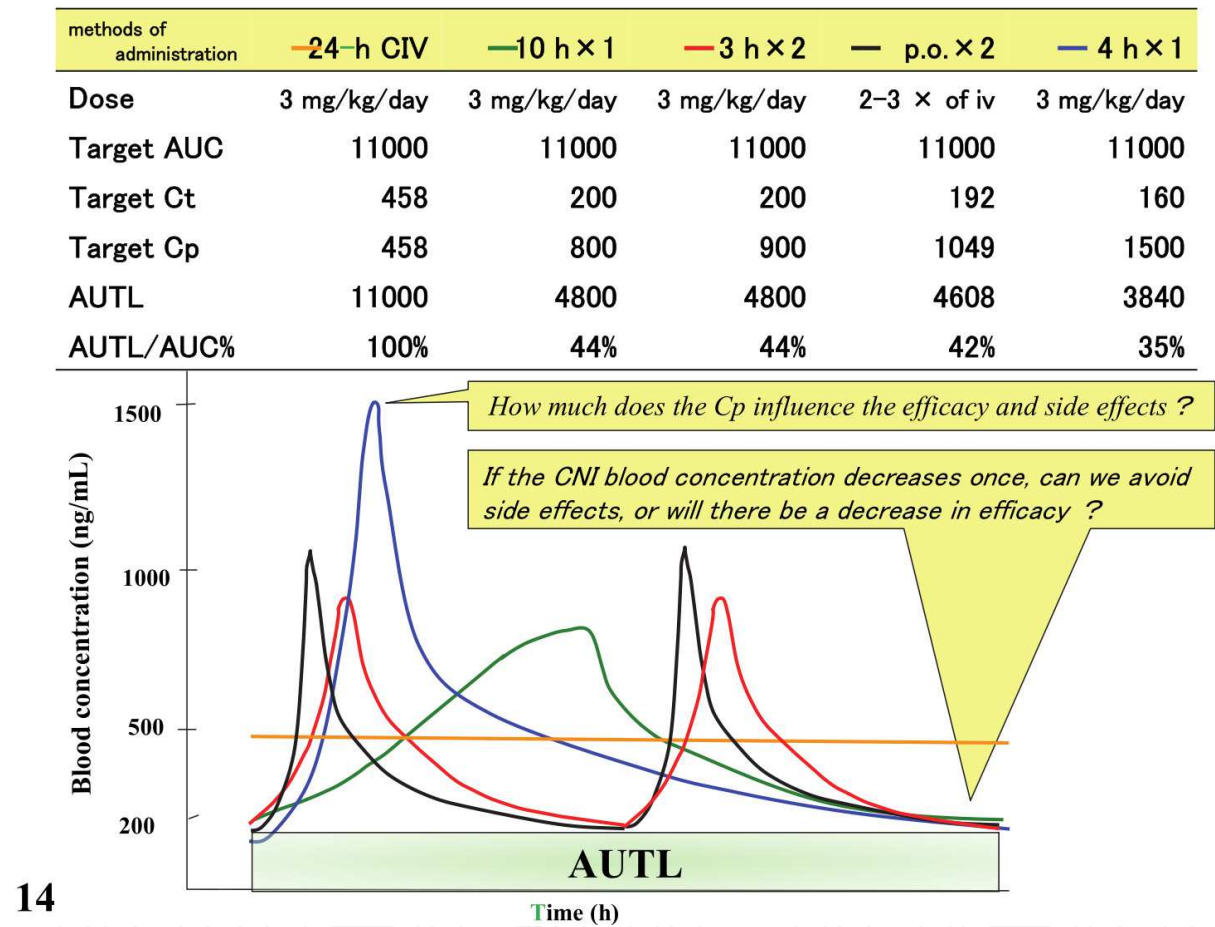
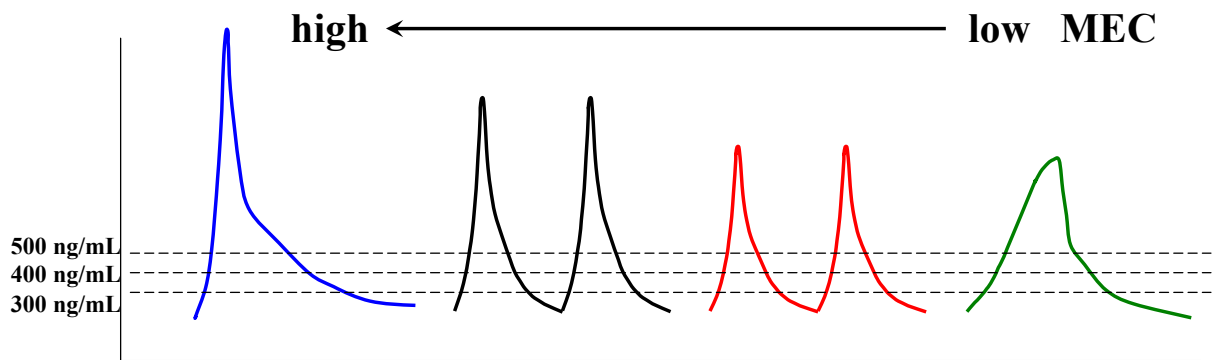


Fig. 9. Comparison of pharmacokinetic parameters among various administration methods of CYA in hematopoietic stem cell transplants.

For TAC, it has already been shown in a clinical trial that numerous side effects, such as nephropathy or neurologic symptoms, are caused by twice daily intermittent intravenous administration. Therefore, the package insert indicates that it should be administered by 24 h continuous intravenous administration, and it is known that continuous intravenous administration is appropriate. It may be because the method for oral use has a large AUTL/AUC% and no high peak, whereas intravenous injection twice a day by high speed drip has a high peak. It is considered that the effect range and the side effect range of TAC

may be closer than those of CYA and that pharmacokinetics showing a gentle blood concentration time curve (large AUTL/AUC%) may be suitable.

| MEC | 24-hCIV | 4 h × 1 | p.o. × 2* | 3 h × 2 | 10 h × 1 |
|-----------|---------|---------|-----------|---------|----------|
| 300 ng/mL | 100% | 73% | 69% | 69% | 69% |
| 400 ng/mL | 100% | 61% | 54% | 51% | 43% |
| 500 ng/mL | 100% * | 51% | 42% | 36% | 27% |



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Fig. 10. T%>MEC of various CYA administration methods for each MEC in hematopoietic stem cell transplants.

6. Pharmacokinetic differences between morning and evening

In studies monitoring the blood concentration of CYA and TAC for 24 h and comparing the pharmacokinetics of morning and evening, some studies reported that there was no difference in pharmacokinetics between morning and evening^{41,42)}, whereas several other studies reported that there was a difference⁴³⁻⁴⁵⁾. In the authors’ data, the AUC₀₋₁₂, AUC₀₋₄, C₂, and C_{max} following evening administration were significant lower than those following morning administration both in patients treated with CYA and patients treated with TAC^{46,47)} (Figure 11). As TAC shows gradual blood concentration–time curve in comparison with CYA, TAC is hardly affected by delayed or reduced absorption in the evening, so that the differences between various PK parameters between morning and evening were smaller in TAC (Table 4). Therefore, a drug such as TAC, which shows pharmacokinetics with a large AUTL/AUC% may have potential benefits because it has little difference in pharmacokinetics between morning and evening. However, a sustained release preparation of TAC administered once a day has been launched and its pharmacokinetics has no peak value in the evening because it is administered only in the morning, but its efficacy is equal to that of a drug administered twice a day. From this fact, it is possible that the pharmacokinetic difference between morning and evening is not a clinical problem.

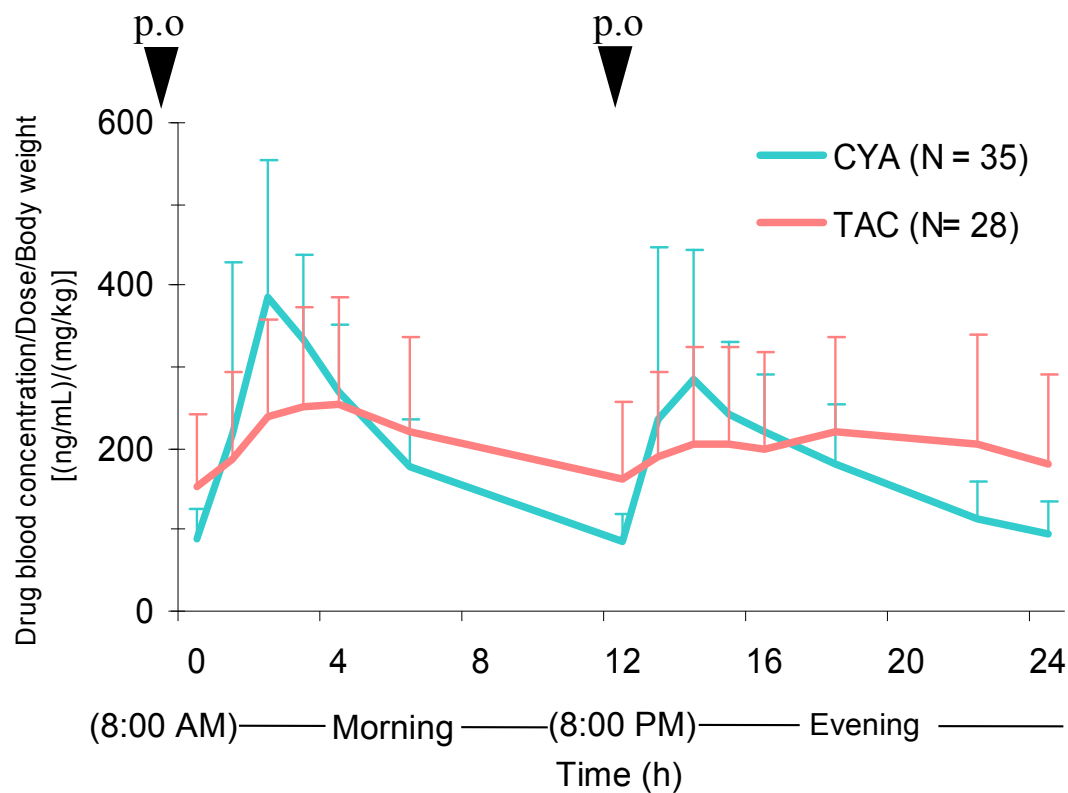


Fig. 11. Comparison of blood concentration-time curves through 24 hours between CYA and TAC.

| | TAC(n=12) | CYA(n=10) | P值 |
|------------------------------------|-----------|-----------|---------|
| AUC ₀₋₁₂ (ng·hr/ml) | 0.91±0.10 | 0.77±0.31 | 0.0073* |
| AUTL/AUC(%) | 1.22±0.18 | 1.42±0.27 | 0.0538 |
| AUC ₀₋₄ (ng·hr/ml) | 0.74±0.14 | 0.56±0.19 | 0.0144* |
| C ₂ (ng/ml) | 0.70±0.31 | 0.51±0.25 | 0.1382 |
| C _{max} (ng/ml) | 0.79±0.26 | 0.55±0.14 | 0.0161* |
| C _{min} (ng/ml) | 1.17±0.21 | 1.28±0.30 | 0.3131 |
| C _{max} /C _{min} | 0.71±0.32 | 0.45±0.16 | 0.0343* |
| T _{max} (hr) | 2.67±1.42 | 1.63±0.80 | 0.0287* |

Table 4. Comparison of pharmacokinetic parameter ratios of evening to morning administrations between TAC and CYA

7. Calculation of optimal dose and blood trough concentration on switching between CYA and TAC

The authors calculated the optimal dose and the C_t concentration on switching between CYA and TAC, with a comparison of the pharmacokinetics (AUC , C_p , and C_t) of CYA and TAC. $AUC/D/BW$ is equal, but the C_t of TAC is relatively higher than that of CYA as a result of the pharmacokinetic differences; considering this, the dosage ratio is as follows: CYA:TAC = 25:1, and the targeted C_t ratio is as follow: CYA:TAC = 13:1^{48,49)} (Figure 12). These reduced values were equal to the titer ratio calculated from the IC_{50} value of the PD data.

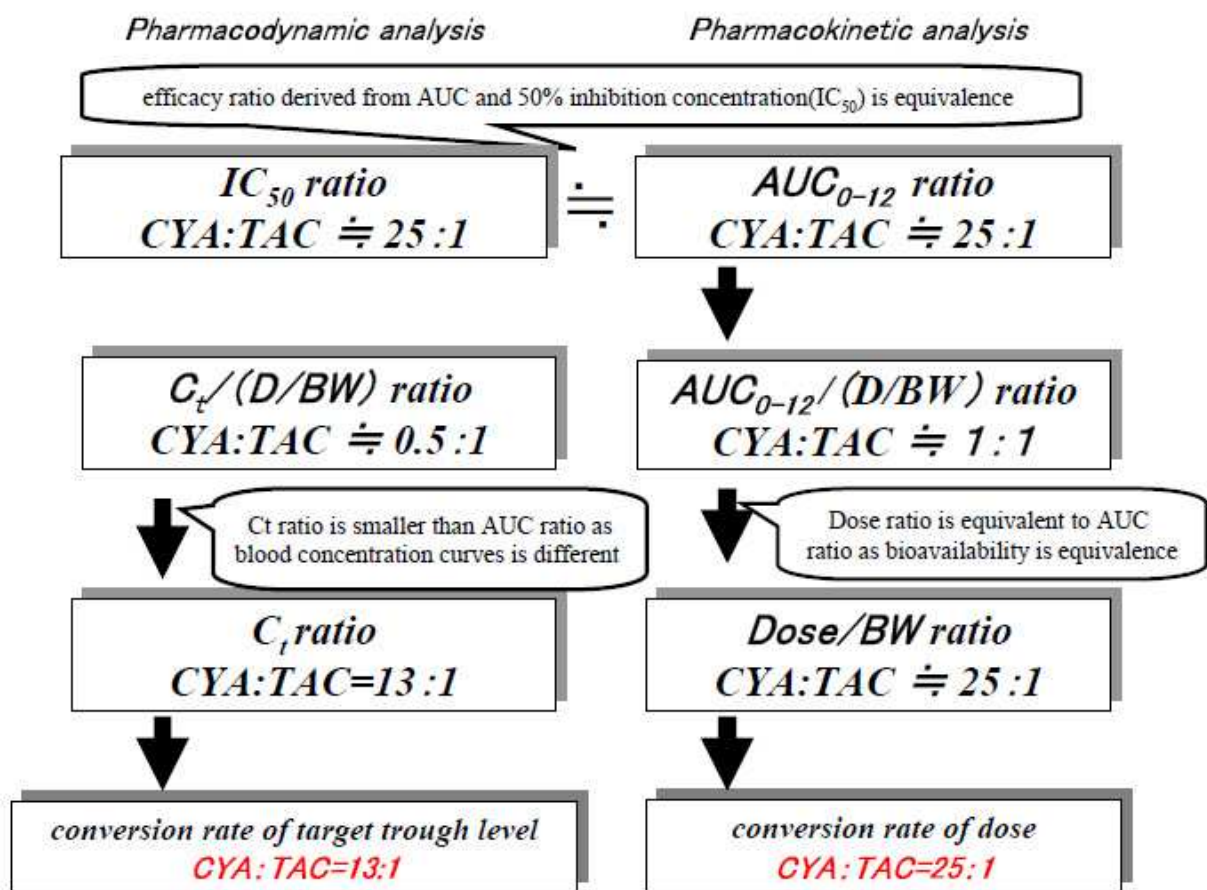


Fig. 12. Conversion rate of dose and target trough level derived from pharmacodynamic and pharmacokinetic analyses.

8. Conclusion

Although both CYA and TAC belong to CNIs and the availabilities ($AUC/D/BW$) are the same, significant differences in the pharmacokinetics (blood concentration-time curve) of both drugs were found. Given that the AUC is the parameter that is most closely associated with clinical effect, it is optimal to monitor C_p and C_t for oral CYA and TAC, respectively.

However, even if both drugs show identical AUC, the clinical effects, such as effectiveness or side effects, may vary according to differences in the blood concentration time curve based on the relative correlation of C_p and C_t . From the report on inhibitory action of CN and blood concentration³²⁾ and the results of PK/PD analysis, It is also thought that CYA status is shown in Figure 13-A. On this basis, it is supposed that the clinical effect of CYA is slightly lower than that of TAC⁵⁰⁻⁵²⁾. It is plausible that the C_t of CYA can be reduced on a temporary basis to avoid nephrotoxicity, as is done with AGs (Figure 13-A). Conversely, there is a possibility that C_p is associated with side effects as shown in Figure 13-B. CYA can reduce the C_p (Figure 13-D) and can also keep the AUC in the blood concentration time curve to elevate the C_t . In fact, CYA shows good results by continuous intravenous infusion for hematopoietic stem cell transplantation³⁸⁾. However, it has been found that there is a slight difference in the clinical results of the hematopoietic stem cell transplantation⁴⁰⁾ (Figure 14). Therefore, CYA has wide tolerance of blood concentration, even if it is administered at various dosages or if it has various blood concentration time curves.

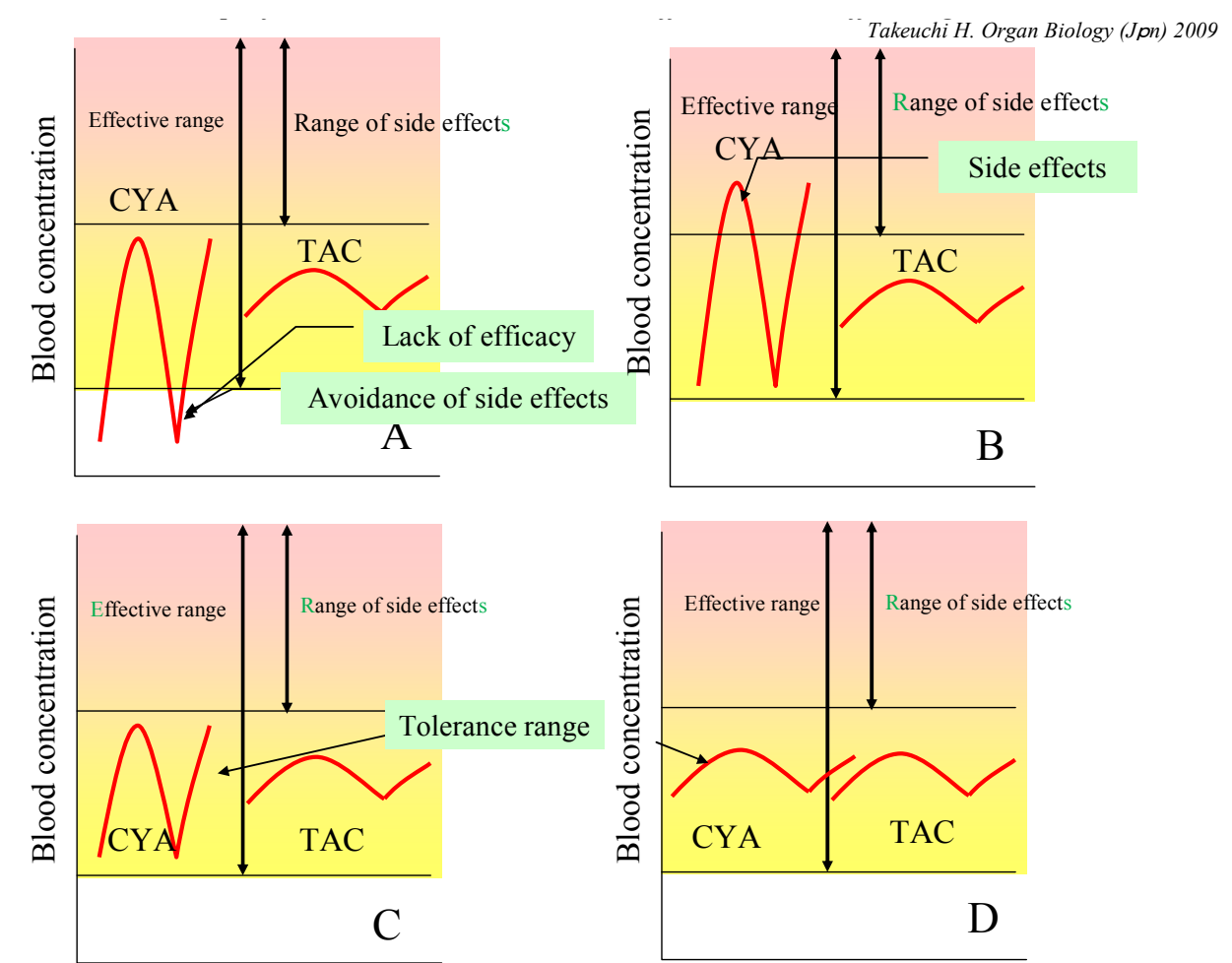
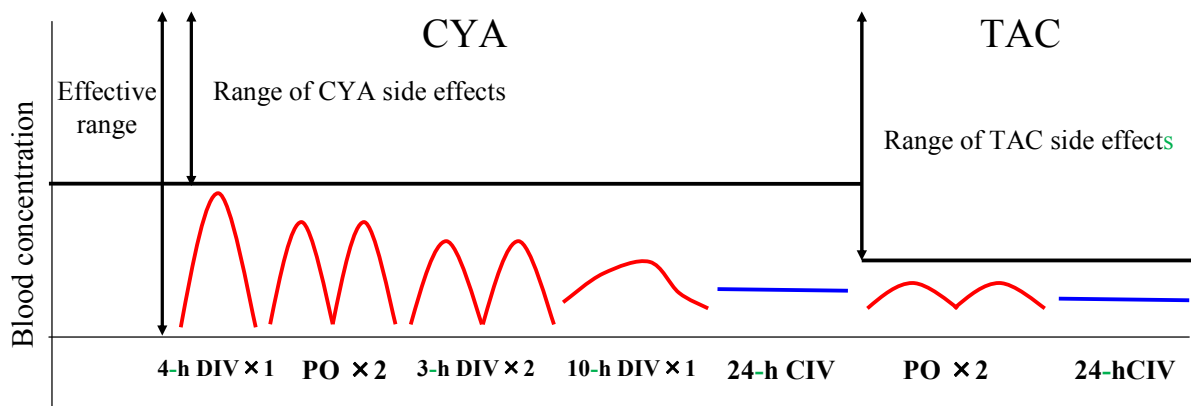


Fig. 13. Various relationships of blood concentration curve and the effective and side effect ranges, when AUCs are equivalent.

CYA and TAC are used equally in clinical practice in terms of the existing therapeutic dose and the AUC, and there are no particular problems (Figure 13-C). On the other hand, it is thought that a gentle (with AUTL/AUC% high) blood concentration time curve is suitable for TAC because its tolerance level is low (Figure 14).



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Fig. 14. Difference in range of effective and side effect blood concentrations between CYA and TAC.

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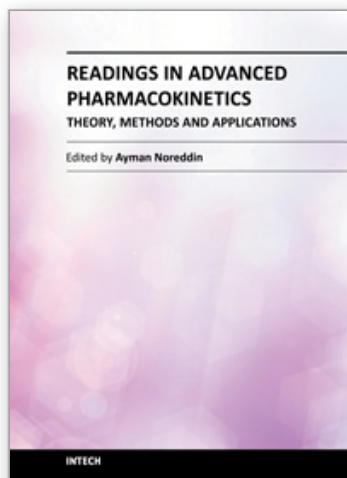
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