Therapeutic drug monitoring of cyclosporine microemulsion in interstitial pneumonia with dermatomyositis

Koji Nagai · Tohru Takeuchi · Takuya Kotani · Kenichiro Hata · Shuzo Yoshida · Kentaro Isoda · Youhei Fujiki · Hideyuki Shiba · Shigeki Makino · Toshiaki Hanafusa

Abstract The prognosis of dermatomyositis (DM)-associated progressive interstitial pneumonia (IP) has recently been improved by steroids/cyclosporine-A (CSA) combination therapy, but treatment outcomes varied. One reason for this variation is thought to be differences in CSA regimen. There is marked interpatient variability in CSA absorption. However, the pharmacokinetics of CSA has rarely been studied. In this study, we calculated the area under the blood concentration–time curve (AUC) of CSA microemulsion in 15 patients with progressive IP complicating DM, and analyzed its correlation with CSA levels at blood sampling time points to investigate the optimum monitoring and dosing regimen. The highest correlation between AUC0–6 and blood level of CSA was observed 2 h (C2) after drug administration ($R = 0.910$). The trough level (C0) was not correlated with AUC 0–6 ($R = 0.052$). There were no differences in blood levels (AUC0–6, C2, and C6) between postprandial administration in a divided dose (CSA given twice daily) and preprandial administration once daily, while C0 was significantly lower ($P = 0.020$) when the drug was administered once daily before breakfast. These findings suggest that measurement of CSA blood level, especially C2 and C0, is useful to monitor clinical and adverse effects of CSA during combination therapy. It is also suggested that preprandial, once daily administration of CSA is beneficial in DM patients with progressive IP.

Keywords Cyclosporine · Dermatomyositis · Interstitial pneumonia · Monitoring

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory muscular disease characterized by heliotrope-like erythema and Gottron’s sign. Interstitial pneumonia (IP) often complicates DM (DM-IP) and progresses acutely/subacutely. It is resistant to steroids, and prognosis is poor [1]. Recent reports have revealed that a combination therapy of steroids and cyclosporine-A (CSA) was effective for progressive DM-IP, but the survival rate (42–69%) and efficacy varied [2–4]. One reason for this variation is thought to be differences in timing of administration and the dose of CSA.

CSA binds to calcineurin with cyclophilin and inhibits T-cell signals, exhibiting an immunosuppressive effect. Absorption of CSA varied widely between individuals, and therefore its blood level is frequently monitored. In the field of transplantation, the area under the blood concentration–time curve (AUC0–4 and AUC0–6) of CSA have been highly correlated with adverse and clinical effects [5, 6]. However, frequent measurement of blood CSA level is necessary to calculate AUC, which is unsuitable for ordinary medical examination. In the transplantation field, the trough level (C0) is measured to prevent adverse drug reactions, and the level at 2 h after administration (C2) has recently been used to achieve immunological effect because of its correlation with AUC [7]. However, no study on pharmacokinetics of CSA has been reported in the field of collagen vascular disease (CVD).

In this study, we initially measured the CSA blood level after oral CSA administration in patients with progressive...
DM-IP, calculated AUC_{0–6}, and identified the optimum blood sampling time point. We also investigated the influence of dosing regimen on the CSA blood level.

**Patients and methods**

**Patients**

Of 29 patients who underwent CSA administration for progressive DM-IP between December 1995 and December 2008, the study was performed in 15 patients in whom AUC_{0–6} could be measured. All 15 patients gave informed consent to this pharmacological study. Oral CSA was administered until December 2005 to 10 patients twice daily, after breakfast and dinner (the divided dose), at a rate of 4.0 mg/kg/day, concomitantly with 1 mg/kg/day prednisolone. From January 2006, 4.0 mg/kg/day CSA was administered once daily (before breakfast) concomitantly with 1 mg/kg/day prednisolone in 5 patients (single dose).

**Measurement of blood concentrations of CSA and calculation of AUC**

Blood samples for AUC determination were collected before administration (C0), and at 2-h intervals for 6 h after CSA administration (C2, C4, and C6, respectively). Blood CSA concentrations were measured by CSA monoclonal whole-blood assay (Cyclosporine-SP-Dynapack, Abbott Laboratories, Chicago, IL, USA) using a fluorescence polarization immunoassay kit. AUC_{0–6} (ng h/ml) was calculated by the trapezoidal method according to the formula

\[
\text{AUC}_{0-6} = C_0 + 2(C_2 + C_4) + C_6.
\]

**Statistical analysis**

Correlations between AUC_{0–6} and C0, C2, C4, and C6 were assessed using the Pearson correlation coefficient. Simple comparisons of the means and standard error (SE) of data were performed using Student’s t test. A P value <0.05 was considered significant. Statistical calculations were performed using JMP version 8.0.

**Results**

**Patient profiles**

Clinical findings, laboratory findings, and CSA treatment of DM patients with progressive IP are listed in Table 1. Their mean age was 55.3 years (range 43–68 years). Poor prognostic factors of DM with progressive IP include clinically amyopathic DM (C-ADM), creatine kinase (CK)/lactate dehydrogenase (LDH) ratio <2, negative test results with anti-Jo-1 antibodies, and presence of pneumomediastinum [2, 8]. Ten patients had C-ADM and CK/LDH ratio <2, 10 patients had negative test results with anti-Jo-1 antibodies, and pneumomediastinum was a complication in 3 of the 15 patients. One patient with postprandial administration of CSA died of IP progression. The mean KL-6 was 1250.9

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Hugh–Jones classification</th>
<th>Complications</th>
<th>Cr (mg/dl)</th>
<th>CK/LDH ratio</th>
<th>Anti-Jo-1 antibody</th>
<th>KL-6 (U/ml)</th>
<th>Drug administration</th>
<th>Cy-A dosage (mg/day)</th>
<th>Outcome</th>
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<tr>
<td>1</td>
<td>61</td>
<td>M</td>
<td>P</td>
<td>V</td>
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<td>191/659</td>
<td>–</td>
<td>3880</td>
<td>Post</td>
<td>200</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>M</td>
<td>P</td>
<td>III</td>
<td>–</td>
<td>0.93</td>
<td>265/344</td>
<td>–</td>
<td>2770</td>
<td>Post</td>
<td>250</td>
<td>Alive</td>
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<tr>
<td>3</td>
<td>47</td>
<td>M</td>
<td>P</td>
<td>IV</td>
<td>Pneumomediastinum</td>
<td>0.67</td>
<td>224/876</td>
<td>–</td>
<td>1220</td>
<td>Post</td>
<td>225</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>F</td>
<td>P</td>
<td>III</td>
<td>–</td>
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<td>194/425</td>
<td>–</td>
<td>512</td>
<td>Post</td>
<td>175</td>
<td>Dead</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>F</td>
<td>D</td>
<td>III</td>
<td>–</td>
<td>0.43</td>
<td>910/960</td>
<td>+</td>
<td>740</td>
<td>Post</td>
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</tr>
<tr>
<td>6</td>
<td>50</td>
<td>F</td>
<td>D</td>
<td>IV</td>
<td>–</td>
<td>0.58</td>
<td>320/451</td>
<td>–</td>
<td>1630</td>
<td>Post</td>
<td>175</td>
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<tr>
<td>7</td>
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<td>F</td>
<td>D</td>
<td>III</td>
<td>–</td>
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<td>13574/1463</td>
<td>+</td>
<td>337</td>
<td>Post</td>
<td>200</td>
<td>Alive</td>
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<tr>
<td>8</td>
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<td>V</td>
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<td>490/726</td>
<td>–</td>
<td>739</td>
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<tr>
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<td>58</td>
<td>F</td>
<td>D</td>
<td>II</td>
<td>Acute respiratory distress syndrome</td>
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<td>1820/811</td>
<td>–</td>
<td>712</td>
<td>Post</td>
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<td>F</td>
<td>P</td>
<td>IV</td>
<td>–</td>
<td>0.58</td>
<td>1549/648</td>
<td>+</td>
<td>366</td>
<td>Post</td>
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<tr>
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<td>54</td>
<td>F</td>
<td>D</td>
<td>IV</td>
<td>–</td>
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<td>3075/665</td>
<td>+</td>
<td>997</td>
<td>Pre</td>
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</tr>
<tr>
<td>12</td>
<td>52</td>
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<td>P</td>
<td>IV</td>
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<td>50/396</td>
<td>–</td>
<td>978</td>
<td>Pre</td>
<td>250</td>
<td>Alive</td>
</tr>
<tr>
<td>13</td>
<td>54</td>
<td>M</td>
<td>P</td>
<td>II</td>
<td>Pneumomediastinum</td>
<td>0.68</td>
<td>530/381</td>
<td>+</td>
<td>1900</td>
<td>Pre</td>
<td>225</td>
<td>Alive</td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>F</td>
<td>D</td>
<td>III</td>
<td>–</td>
<td>0.4</td>
<td>257/269</td>
<td>–</td>
<td>713</td>
<td>Pre</td>
<td>275</td>
<td>Alive</td>
</tr>
<tr>
<td>15</td>
<td>58</td>
<td>F</td>
<td>P</td>
<td>IV</td>
<td>–</td>
<td>0.45</td>
<td>553/438</td>
<td>–</td>
<td>1270</td>
<td>Pre</td>
<td>200</td>
<td>Alive</td>
</tr>
<tr>
<td>Average</td>
<td>55.3</td>
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</table>

P probable DM; D definite DM; Cr creatinine; CK creatine kinase; LDH lactate dehydrogenase; Post postprandial, twice daily in a divided dose; Pre preprandial, once daily before breakfast in a single dose
U/ml (range 337–3880 U/ml). The mean level of serum creatinine was 0.57 mg/dl (range 0.40–0.93 mg/dl). The mean dosage of CSA at the start of treatment was 208.3 mg/day (range 175–275 mg/day).

Pharmacokinetics of CSA in individual patients

The pharmacokinetics of CSA in individual patients is shown in Fig. 1. Mean ± standard deviation (SD) AUC 0–6 was 4075.0 ± 1454.9 ng h/ml. Mean ± SD blood concentrations were as follows: C0, 157.3 ± 41.4 ng/ml; C2, 1222.6 ± 523.8 ng/ml; C4, 566.0 ± 202.7 ng/ml; C6, 340.7 ± 160.2 ng/ml. In all of the patients, the CSA peak concentration appeared at 2 h after administration (C2).

![Fig. 1 Pharmacokinetics of cyclosporine in individual patients. Solid and broken lines represent patients with preprandial and postprandial administration, respectively](image)

Correlation of AUC 0–6 with C0, C2, C4, and C6

Correlations of AUC 0–6 with C0, C2, C4, and C6 are shown in Fig. 2. C2, C4, and C6 correlated significantly with AUC 0–6 ($R = 0.910$, 0.603, and 0.673; $P < 0.0001$, 0.0007, and 0.0002). The strongest positive correlation was noted between AUC 0–6 and C2 ($R = 0.910$; $P < 0.0001$). C0 did not correlate with AUC 0–6 ($R = 0.052$).

Comparison of CSA blood level between daily postprandial administration in a divided dose and a single dose before breakfast

CSA blood level is compared between postprandial administration in a divided dose and a single dose before breakfast in Fig. 3. The CSA C0 level was significantly lower when administered once daily before breakfast than when administered in the divided dose after meals ($P = 0.020$). There were no differences in blood levels (AUC 0–6, C2, and C6) between administration in the divided dose after meals and once daily.

Discussion

We investigated the pharmacokinetics of CSA in patients with progressive DM-IP. Blood CSA level peaked at C2 in all patients. AUC 0–6, which most markedly reflects the immunosuppressive effect, was significantly correlated with all sampling points after CSA administration, especially C2, but not C0. It has also been reported that AUC most strongly correlated with C2 while it was not correlated with C0 in the transplantation field [7] and that AUC was correlated with C2 in psoriasis and nephritic syndrome.
Our study is the first report to reveal the dynamics of the blood CSA level in the field of CVD, in which the importance of C2 monitoring was clarified. A standard regime of CSA/steroids combination therapy for progressive DM-IP has not been established. It has been reported that prognosis is favorable and respiratory function improved when CSA administration is initiated early after diagnosis of DM-IP [2, 4, 11]. The dosage of CSA for DM-IP was 100–300 mg/day in these previous reports. We previously treated 16 progressive DM-IP patients with steroids and CSA in an early stage and found that the outcome was more favorable when the dose of CSA was high [4]. Combining these findings with those of the present study, blood CSA level should be controlled based on C2, because the CSA absorption rate varies markedly among individuals.

The CSA C2 level is controlled at about 800 ng/ml in the field of transplantation [12], and an increase in the incidence of adverse effects at a CSA C0 level exceeding 200 ng/ml has been reported [13]. In this study, the mean CSA C2 and C0 levels were 1128.8 and 157.3 ng/ml, respectively. Infection could be treated by repeated surveillance and early treatment without development of drug-induced severe adverse events. Further investigation is needed to reveal the association between clinical and adverse effects and the CSA level in the blood, particularly regarding C0 and C2.

The dosing regimen of CSA may influence the blood CSA level. We compared the blood level between the postprandial divided dose and preprandial once-a-day dose groups. C2 was the peak blood level in both groups, and there were no differences in the blood levels (AUC0–6, C2, and C6) between the once-a-day group and the divided dose group, while C0 was significantly lower in the once-a-day group. As recently proposed in the transplantation and the nephritic syndrome fields, preprandial, once daily administration may be more useful than postprandial administration in divided doses [14, 15]. Our data support these proposals.

CSA has recently been used for CVD-associated IP, in addition to DM-IP. Considering the marked individual variation in pharmacokinetics of CSA, measurement of its blood level, particularly C0 and C2, is necessary to evaluate clinical and adverse effects of CSA. It was also suggested that preprandial, once daily administration is more useful to achieve maximal immunosuppressive effect and avoid adverse events. However, the sample size of this study was limited, and DM patients with IP refractory to the combination of steroids and CSA have also been reported. Further studies are needed to establish a standard therapeutic strategy for DM-IP.

Conflict of interest None.

References

5. Mahalati K, Belitsky P, Sketris I, West K, Panek R. Neoral monitoring by simplified sparse sampling area under the


