Effect of single-dose rituximab on steroid-dependent minimal-change nephrotic syndrome in adults

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ABSTRACT

Background. Steroid-dependent minimal-change nephrotic syndrome (MCNS) requires administration of prolonged courses of prednisolone (PSL); therefore, a paradigm shift from such toxic 'non-specific' therapies to selective immunomodulating regimens is necessary for these cases.

Methods. To assess the therapeutic effects of rituximab (an anti-CD20 antibody) in adult patients with steroid-dependent MCNS, we performed a prospective trial of the effects of a single dose of rituximab administered twice at an interval of 6 months in 25 MCNS patients. We evaluated the biochemical parameters and compared the clinical findings between the 12-month period before and 12-month period after the first rituximab infusion.

Results. A significant reduction in the number of relapses and the total dose of PSL administered was observed during the 12-month period after the first rituximab infusion when compared with the findings during the 12-month period before the first rituximab infusion [25 (100%) versus 4 (16%), P < 0.001; 8.2 versus 3.3 g, P < 0.001; 26.4 mg/day at baseline versus 1.1 mg/day at 12-month, P < 0.0001]. Complete remission was achieved/maintained in all patients undergoing B-cell depletion. Four of 17 patients with B-cell repletion developed relapse.

Conclusions. Our results revealed that rituximab therapy was associated with a reduction in the number of relapses and in the total dose of PSL needed. Therefore, rituximab appears to be a useful therapeutic agent for adult patients with steroid-dependent MCNS. These results suggest that this treatment is rational and should be considered as an important option in the management of adult patients with steroid-dependent MCNS.

INTRODUCTION

Patients with steroid-dependent minimal-change nephrotic syndrome (MCNS) are usually treated with steroids and
immunosuppressants, such as cyclosporine (CyA), cyclophosphamide (CPA) and mycophenolate mofetil (MMF). While MCNS is known to be associated with a good renal prognosis, some patients show frequent relapses. The reported relapse rates in cases of adult-onset MCNS vary from 30 to 80%, and our previous data suggests a relapse rate of 67.1% [1, 2]. Therefore, patients often suffer from steroid toxicities such as cataract, diabetes and osteoporosis. Immunosuppressive drugs also have significant adverse effects. Chronic nephrotoxicity is a well-known side effect of CyA, and long-term use of this drug is known to be associated with a high risk of developing chronic CyA nephrotoxicity [3], although Kranz et al. [4] reported that the long-term use of CyA is relatively safe. Because of the possibility of gonadotoxicity (azoospermia), it is recommended that CPA be used within limited cumulative doses. The use of mizoribine (MZ) and MMF is still off-label for the treatment of nephrotic syndrome in Japan, although both have been shown to be relatively safe and effective immunosuppressants. Therefore, prolonged use of these drugs is difficult, even if they prove to be effective.

Recent studies have reported that rituximab may be effective for the treatment of nephrotic syndrome [5–9]. Rituximab is a chimeric monoclonal antibody that acts by inhibiting CD20-mediated B-cell proliferation and differentiation, and induces a profound depletion of CD20- and CD19-positive cells through both complement-mediated lysis and antibody-dependent cell-mediated cytotoxicity. The CD20 antigen is a membrane protein that is expressed on the B-cells. The drug was first introduced in the late 1990s for the treatment of B-cell non-Hodgkin’s lymphoma [10]. Since then, it has been used for the treatment of several immunological disorders caused by autoantibodies [11, 12]. The most commonly reported side effect of rituximab infusion is infusion reaction, such as rash and chills. Even though other severe side effects of rituximab are not common, physicians must be aware of its potentially life-threatening side effects, including progressive multifocal leukoencephalopathy, fatal lung fibrosis and severe colitis [13, 14].

The pathophysiological process of MCNS remains poorly understood. However, experimental and clinical data suggest that this disease is the consequence of an immune disorder causing increased glomerular permeability and albuminuria. According to the currently accepted concept, which dates back to the mid-1970s, abnormal T-cell function is the keystone. This concept was reinforced later by the observation that systemic infusion of supernatants of T-lymphocytes from patients with MCNS induced proteinuria in rats [15]. To date, despite extensive research, the permeability factors are still unknown, and the pathophysiological process of MCNS remains unclear. B-lymphocytes may play an important role in the pathogenesis of MCNS because of reports to the beneficial effects of rituximab as a rescue therapy in children with steroid-dependent MCNS [5, 6]. We evaluated the usefulness of rituximab in the treatment of steroid-dependent MCNS in adults.

### MATERIALS AND METHODS

#### Patient population

Patients fulfilling the following criteria were enrolled in this study: (i) steroid-dependent nephrotic syndrome was defined as episodes characterized by the occurrence of relapse during the tapering down or within 2 weeks of discontinuation of prednisolone (PSL). Nephrotic syndrome was defined as proteinuria ≥3.5 g/day, serum albumin <3.0 g/dL, oedema and hyperlipidaemia. A patient was defined as showing ‘relapse’ when the trial nephrologists judged it necessary to step up the immunosuppressive therapy, supported by a daily urinary protein excretion of ≥3.5 g with 3+ or 4+ results on the urine albumin dipstick test for albumin; (ii) biopsy-proven diagnosis of minimal-change disease (MCD); (iii) no known associated systemic disease; negative serology for hepatitis B and C, HIV and antinuclear antibodies; no positive family history. It is noteworthy that the distinction between primary and secondary glomerulonephritis was not established by histology alone, but by a combination of the available clinical data. (iv) No previous history of rituximab treatment. The study was conducted with the approval of the Research Ethics Board of Tokyo Women’s Medical University. All the patients gave written informed consent for participation in the study. Between March 2008 and May 2010, 25 patients (19 male and 6 female) with steroid-dependent MCNS were enrolled for the study at our department. The clinical characteristics of all the patients are shown in Table 1 and Figure 1.

The mean duration from the diagnosis until the start of rituximab treatment was 10 ± 8 years. All of the patients experienced relapse and the total number of relapses was 62 times during the 12-month period before the first rituximab injection. Eight patients (32%) had nephrotic syndrome, eight patients (32%) were in partial remission and nine patients (36%) had complete remission at initiation of rituximab treatment. ‘Complete remission’ was defined as clinical improvement supported by a daily urinary protein excretion of <0.3 g and trace or negative urine dipstick test for albumin. ‘Partial remission’ was defined by a daily urinary protein excretion of <3.5 g, below nephrotic range, with an increase in the serum albumin. All patients who had experienced relapse during the 12-month period before rituximab treatment required an increase in the PSL dose. All 16 patients with nephrotic syndrome or partial remission had their steroids increased when they relapsed. In 18 of the 25 patients, re-biopsy was performed, which revealed MCD. The mean age of the patients at the start of rituximab treatment was 30 ± 12 years. The clinical data were examined according to the presence/absence of history of treatment with steroids and/or conventional immunosuppressants. Previous immunosuppressive drug use included CyA in 20 patients, MZ in 5 patients, MMF in 3 patients and 25 patients were receiving a steroid (PSL 26.4 ± 11.5 mg/day; range 10–60 mg/day) at the start of rituximab treatment.
Treatment

Before administration of rituximab, the following laboratory examinations were performed: complete blood count, serum biochemistry [serum albumin (Alb), serum creatinine (Cr), serum immunoglobulin levels (IgG, IgA, IgM), urinary protein (UP), peripheral B-cell counts (CD19, CD20)] and CD4/8 counts. In addition, because MCNS is a Th2-dependent glomerular disease [16], we measured the Th1/Th2 ratio and the levels of cytokines [interleukin-4 (IL-4) and tumour necrosis factor-α (TNF-α)] related to the Th1/Th2 ratio [17, 18].

The first rituximab dose was administered by intravenous injection at a single dose of 375 mg/m² body surface area (BSA) (maximum, 500 mg). In order to minimize infusion reactions, we administered betamethasone at the dose of 4 mg.

**Table 1. Changes in clinical parameters in steroid-dependent MCNS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(1st Rituximab)</th>
<th>(2nd Rituximab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
</tr>
<tr>
<td>Sex (female: male)</td>
<td>6:19</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30 ± 12</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>119 ± 13</td>
<td>116 ± 13</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74 ± 12</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Urinary protein (g/day)</td>
<td>2.5 ± 3.5</td>
<td>0.5 ± 1.4*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4 ± 0.8</td>
<td>4.0 ± 0.8*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>285 ± 86</td>
<td>239 ± 57</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.1</td>
</tr>
<tr>
<td>CD19 (/mm³)</td>
<td>126 ± 134</td>
<td>1.6 ± 1.4*</td>
</tr>
<tr>
<td>CD20 (/mm³)</td>
<td>134 ± 136</td>
<td>1.4 ± 1.2*</td>
</tr>
<tr>
<td>The depletion of B cell (n)</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>CD4/8</td>
<td>1.3 ± 0.7</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>IL-4</td>
<td>15.2 ± 16.8</td>
<td>14.0 ± 19.0</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.5</td>
</tr>
<tr>
<td>Th1/Th2</td>
<td>24.3 ± 31.6</td>
<td>20.5 ± 19.6</td>
</tr>
<tr>
<td>Nephrotic syndrome (n)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Complete remission (n)</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Number of patients taking PSL (n)</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Dosage of PSL (mg/day)</td>
<td>26.4 ± 13.5</td>
<td>18.2 ± 11.0*</td>
</tr>
<tr>
<td>Number of patients taking CyA (n)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Dosage of CyA (mg/day)</td>
<td>110 ± 43</td>
<td>96 ± 38</td>
</tr>
</tbody>
</table>

*P-value: significantly different from baseline. Values are expressed as mean ± SD. P<0.05. PSL, prednisolone; CyA, cyclosporine.
acetaminophen at the dose of 200 mg and cyproheptadine hydrochloride at the dose of 4 mg to the patients 30 min prior to the rituximab infusion. In addition, after 6 months, the second rituximab infusion was administered by the same method (Figure 2).

**Follow-up**

In all patients, the clinical and laboratory parameters, including a complete blood count, biochemical parameters, serum levels of IL-4 and TNF α, peripheral blood CD4/8 counts and Th1/Th2 ratios, and the CD19 and CD20 B-cell counts as determined by flow cytometry were examined. An attempt was made to taper the dose/discontinue steroids by 12 months after the first rituximab injection, although no precise protocol was set for tapering the steroid dose. There were no restrictive protocols for discontinuation of either the immunosuppressants or PSL in this trial. Patients were followed up for at least 12 months after the first rituximab injection. The changes in the laboratory parameters, dose of PSL, frequency of complete remission, frequency of relapse, presence/absence of nephrotic syndrome, degree of B-cell depletion and B-cell repletion and dosages of PSL and CyA recorded at the baseline and at 1, 3, 6, 9 and 12 months after the rituximab injection were evaluated. B-cell depletion was defined as a peripheral blood CD19 count of <10/mm³ and B-cell repletion was defined as a peripheral blood CD19 count of >10 mm³. In addition, the cumulative dose of PSL, number of patients requiring PSL, CyA, MMF or MZ and the total number of relapses were evaluated at the baseline, during the 12-month period before the baseline and during the 12-month period after the baseline.

**Statistical analysis**

Data were expressed as means ± standard deviation (SD). All analysed variables were tested for distribution. The t-test was used for samples with a normal distribution and the Mann–Whitney U-test was used for samples with a skewed distribution to analyse the differences in the laboratory data recorded at the baseline and at 1, 3, 6, 9 and 12 months after the rituximab injection. Categorical data, frequency of complete remission, frequency of relapse, presence/absence of nephrotic syndrome, number of patients requiring PSL, CyA, MMF or MZ and the total number of relapses, were analysed using the χ² test. All statistical analyses were performed using the JUMP 8 software (SAS Institute, Cary, NC). Statistical significance was established at P < 0.05.

**RESULTS**

All 16 patients with nephrotic syndrome or partial remission at the start of rituximab treatment had complete remission within 1 month. The number of patients with relapse, the total number of relapses and the cumulative dose of PSL and CyA were compared between the 12-month period before
rituximab injection and the 12-month period after rituximab injection. The number of patients with relapse and the total number of relapses were significantly lower (4 versus 25; P < 0.001, 4 versus 62; P < 0.001) and the cumulative dose of PSL, the number of patients requiring CyA were also significantly lower [8.2 ± 3.4 versus 3.3 ± 2.3 g (P < 0.001); 20 versus 6 (P < 0.001)] during the 12-month period after rituximab than during the 12-month period before the rituximab injection (Table 2).

The results revealed an absence of any significant changes in blood pressure, Cr, IgA, IgM, CD4/8 ratio, Th1/Th2, serum IL-4 or TNF-α. Significant decreases in the UP, total cholesterol and CD19/CD20 counts were found at 12 months (0.5 ± 2.2 g/day, 188 ± 48 mg/dL, 39 ± 137 and 33 ± 103/mm³, P = 0.04, 0.002, 0.04 and 0.04, respectively) when compared with the values at the baseline (2.5 ± 3.5 g/day, 285 ± 86 mg/dL, 126 ± 134 and 134 ± 136/mm³, respectively). Significant increases in the serum Alb and IgG levels were noted at 12 months after the first rituximab injection (4.2 ± 0.3 g/dL and 1001 ± 230 mg/dL, P = 0.01 and 0.0005, respectively) when compared with the levels at baseline (3.4 ± 0.8 g/dL, 707 ± 191 mg/dL). The CD19 and CD20 counts were also significantly decreased and the number of patients with the depletion of B-cell was significantly increased at 1 month [from 126 ± 134 to 1.6 ± 1.4/mm³ (P = 0.0001), 134 ± 136 to 1.4 ± 1.2/mm³ (P < 0.0001) and 0 to 25 (P < 0.0001), respectively], 3 months [2.8 ± 6.1/mm³ (P < 0.0001), 2.8 ± 7.4/mm³ (P < 0.0001); and 25(P < 0.0001), respectively] and 6 months [20 ± 48/mm³ (P = 0.003), 22 ± 46/mm³ (P = 0.007) and 15 (P < 0.0001), respectively] after the first rituximab injection and also at 9 months [5.3 ± 9.0/mm³ (P < 0.0001), 4.7 ± 7.9/mm³ (P < 0.0001) and 25 (P < 0.0001), respectively] after the second rituximab injection.

Although complete B-cell depletion was achieved after 1 month, the peripheral B-cell counts significantly increased at 6 months after the first single-dose injection of rituximab in 10 of the 25 patients and also significantly increased at 12 months (i.e. after the second single-dose injection of second rituximab) in 5 of the 25 patients (Table 1). There were three patients (12%; No. 4, No. 10, No. 23) who developed relapse by around 6 months after the first rituximab infusion, and one patient (4%; No. 1) who developed relapse by around 6 months after the second rituximab infusion (Figure 1). One patient (No. 10) was restarted on PSL 20 mg/day followed by the second rituximab infusion, and three patients (No. 4, No. 10 and No. 23) were administered the second rituximab infusion without restarting/increasing the dose of PSL. All of the patients who developed relapse were revealed to have B-cell repletion. The CD19 or 20 counts in the patients who developed relapse (No. 1, No. 4, No. 10, No. 23) increased significantly (209 ± 312, 167 ± 229/mm³, P < 0.0001) when compared with that in those who did not develop relapse (18 ± 38, 18 ± 38/mm³) at 6 months after rituximab injection.

The steroid could be discontinued at 12 months after the first rituximab administration in 21 of the 25 patients who were receiving a steroid at the start of the study treatment. In
all patients, the PSL dose could be tapered after the administration of rituximab. However, one patient (No. 10) of four patients with relapse was restarted on PSL 20 mg/day at the second rituximab infusion. The mean PSL dose decreased significantly at 12 months after the rituximab administration [from 26.4 ± 11.5 mg/day (range 10–60 mg/day) at baseline to 1.1 ± 2.8 mg/day at 12 months; P < 0.0001]. The CyA dose could be reduced significantly from 110 ± 43 mg/day at baseline to 30 ± 48 mg/day (P < 0.0001) at 12 months after the first rituximab injection.

The MMF and MZ could be discontinued at 12 months after the first rituximab administration.

Five patients (24%) experienced adverse effects, including mild infusion reactions such as cough and hiccough, which did not necessitate treatment withdrawal in three patients. One patient almost immediately developed exanthema during the administration of rituximab. The pattern of exanthema was observed as a fixed drug eruption on the trunk and improved once again following the administration of betamethasone. One patient (No. 16) developed leukopaenia (white blood cell 3000/mm³) at 9 months, and the white blood cell count improved to 5000/mm³ at 12 months.

**DISCUSSION**

In patients with steroid-dependent MCNS, repeated courses of treatment with high doses of PSL are necessary. In our previous study, the relapse group showed a significantly higher frequency of steroid side effects, such as osteoporosis, when compared with the non-relapse group [1]. However, new immunomodulatory agents have been used in the treatment of steroid-dependent MCNS, although the precise nature of mechanism underlying their effects remains unknown. It is now clear that there is a need for newer and effective, yet safe, agents for the treatment of steroid-dependent MCNS. Rituximab, a chimeric anti-CD20 monoclonal antibody, which is known to cause B-cell depletion, has been shown to have significant efficacy against immunological disorders caused by autoantibodies [12]. Several reports have suggested the possible efficacy of rituximab in childhood patients with nephrotic syndrome [5–9]. Adult-onset MCNS is known to be associated with a higher prevalence of hypertension, renal impairment and a slower response to steroids, but also a lower tendency to relapse; however, relatively little is known about MCNS in older adults [9]. There are no previous reports of clinical trials of rituximab in adult patients with steroid-dependent MCNS. In regard to case reports, François et al. [8] demonstrated the efficacy of rituximab in a patient with MCNS diagnosed at the age of 6 years and treated with rituximab at the age of 23 years after frequent relapses and treatment failures with other agents. Thus, chronic childhood MCNS persisting into adulthood may respond to rituximab, and sustained remissions with rituximab are possible, despite long-term disease. In addition, Yang et al. [19] described that the onset of MCNS in older adults has similar clinical presentations and shares similar rates of steroid responsiveness and response to rituximab to their younger counterparts. In contrast, Peters et al. [20] described that a second course of rituximab was ineffective in a 20-year-old female with relapsing MCNS first diagnosed at the age of 2 years. In our study, the efficacy of rituximab in adults with steroid-dependent MCNS was almost the same as that observed for the childhood form of the disease.

In most previous studies, rituximab was given at the dose of 375 mg/m² BSA once a week for 4 weeks [7, 10]. However, Smith [21] reported successful treatment of a patient of steroid-dependent nephrotic syndrome (SDNS) with a single dose of rituximab. In addition, Kamei et al. [6] reported a prospective study of the efficacy of a single dose of rituximab for refractory SDNS. We also successfully treated primary glomerular disease with a single dose of rituximab [22–25]. Therefore, we conducted a prospective study to examine the efficacy and safety of a single dose of rituximab for adult patients with steroid-dependent MCNS.

Most of the relapses developed simultaneously with the recovery of the B-cell counts [6]. In a study by Guigonis et al.

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**Table 2. Clinical characteristics of patients with steroid-dependent MCNS between periods of 12 months before rituximab and periods of 12 months after rituximab**

<table>
<thead>
<tr>
<th></th>
<th>Pre-rituximab</th>
<th>Post-rituximab</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSL(n)</td>
<td>25</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The cumulative dose of PSL (g)</td>
<td>8.2 ± 3.4</td>
<td>3.3 ± 2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CyA (n)</td>
<td>20</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMF (n)</td>
<td>3</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>MZ (n)</td>
<td>5</td>
<td>0</td>
<td>0.05</td>
</tr>
<tr>
<td>Relapse (n)</td>
<td>25</td>
<td>4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD; P-value: significantly different between periods of 12 months during pre-rituximab and periods of 12 months during post-rituximab. NS, not significant; PSL, prednisolone; CyA, cyclosporine. The cumulative dose of PSL in pre-rituximab was calculated total dose during the 12-month periods before first rituximab. The cumulative dose of PSL in post-rituximab was calculated total dose during the 12-month periods after first rituximab.
the efficacy of rituximab was assessed in 22 patients with SDNS and steroid-resistant nephrotic syndrome, including patients with MCD and focal segmental glomerulosclerosis. No relapse of proteinuria was recorded during the B-cell depletion period. Relapses occurred when the CD19/mm³ count increased to between 54 (3% of the total lymphocyte count) and 273 (7%). In non-relapsing patients, rituximab doses were repeated when the CD19/mm³ counts were between 10 (1%) and 270 (7%), in accordance with therapeutic guidelines [5]. The time to recovery of B-cells ranged from 5 to 10 months (average 7.5 months). Retreatment was performed in all patients about 6 months after the first rituximab infusion in our study, and remission was maintained in all patients undergoing B-cell depletion (Figure 2). One patient (No. 1) relapsed at 6 months after retreatment.

This observation suggests that suppression of B-cells might be involved in the pathophysiology of MCNS. Since MCNS is not an antibody-mediated disease, the success of rituximab may seem surprising. B-lymphocytes may play an important role in the pathogenesis of MCNS. B-cells play an important role as immunoregulatory cells by both antigen presentation and induction of cytokine release. Their elimination could have dampening effects on other immune cells, such as T-lymphocytes, dendritic cells or macrophages. Assuming that relapse occurred after increase in the count of CD19/20-positive B-cells, single-dose rituximab injections could possibly be given repeatedly. It is necessary to establish a precise protocol for rituximab therapy in adult patients with steroid-dependent MCNS. The protocol for administration of single-dose rituximab twice each year might allow remission to be sustained without administration of PSL or immunosuppressants.

The present study results appear to suggest the efficacy of rituximab in the treatment of steroid-dependent MCNS. There were no severe acute injection reactions during the observation period. However, a longer follow-up is required in order to evaluate adverse events such as multifocal progressive leukoencephalopathy. Rituximab therapy can facilitate reduction in the steroid dose.

In conclusion, a single dose of rituximab was used for the treatment of steroid-dependent MCNS, with mostly favourable outcomes and no serious adverse events. However, the follow-up period of the patients in this study was relatively short. Therefore, further evaluation and randomized controlled trials are required to evaluate the benefits of long-term use of rituximab in the treatment of steroid-dependent MCNS.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES


Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients

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ABSTRACT

Background. Calciphylaxis is a life-threatening complication in patients with end-stage renal disease (ESRD). No established therapy exists so far. The aim of the present study was to determine the therapeutic response to a multi-interventional treatment regimen with consistent use of sodium thiosulphate (STS) in an Austrian cohort of calciphylaxis patients.

Methods. We retrospectively collected demographic, clinical and laboratory data on 27 calciphylaxis patients treated with STS at seven Austrian dialysis centres between June 2004 and November 2010.

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