Cyclophosphamide: effective in the treatment of severe cutaneous involvement in systemic sclerosis

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a rheumatologic disease characterized by autoimmune inflammation, vasculopathy and tissue fibrosis of skin and various organs. There are few effective treatments available for a severe cutaneous involvement of diffuse SSc. Therefore, we evaluated the efficacy of cyclophosphamide in the treatment of severe diffuse SSc. Patients and methods: Nine diffuse SSc (American College of Rheumatology [ACR] criteria) patients with a modified Rodnan skin score (MRSS) > 30 (0-51) were submitted to treatment with cyclophosphamide (CPM), at a monthly dose of 0.5 to 1.0 g/m² IV for 18 months. MRSS was performed every six months during 18 months. Laboratory evidence of inflammatory activity and adverse events were also retrospectively assessed. Patients with severe pulmonary and cardiac involvement were excluded. Results: Most patients were female (77%) with mean age of 41.7 years and duration of disease of 2.2 years. There was a significant reduction in the MRSS from 37.7 ± 4.08 to 29.1 ± 8.13 after 12 months of treatment (P = 0.009). Seven patients completed 18 months of CPM and had persistent reduction of the MRSS (mean MRSS = 26.4. P = 0.01). There was also a reduction of C-reactive protein (CRP) (initial mean CRP = 8.9 mg/dL) compared with values after 18 months of treatment (mean CRP = 3.09 mg/dL, P = 0.04). There were no infections, urinary disorders and/or important hematological problems throughout the treatment. Conclusion: The treatment with cyclophosphamide was effective and should be considered an alternative for the treatment of severe cutaneous involvement of SSc.

Keywords: Systemic sclerosis, treatment, cyclophosphamide, modified Rodnan skin score, treatment.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease of yet unknown cause and of difficult treatment. Its pathogenesis is based in an autoimmune inflammatory process, systemic vasculopathy and collagen deposits in the skin and internal organs leading to tissue fibrosis with severe functional consequences and an important increase of mortality. Currently, the main cause of death for SSc is pulmonary onset, involving both the interstice and the vasculature.

The cutaneous involvement, especially in the diffuse form of the disease (dSSc), can be extensive and lead to a severe functional limitation and reduction in the quality of life. With the objective of evaluating the effectiveness of novel treatments, semiquantitative involvement measures of skin by the modified Rodnan score (MRSS)¹ have been utilized. This clinical score of easy execution seems to reflect well the severeness of the cutaneous involvement once there is a direct correlation between MRSS and the grade of collagen deposition evaluated by cutaneous biopsies.²

In addition, the extension of the cutaneous fibrosis is directly associated to a greater involvement of internal organs and this reflects a part of the patients with greater severeness and mortality.³,⁴
The treatment of systemic sclerosis, particularly the diffuse form of the disease, remains a great medical challenge and various therapies were evaluated with the objective of reducing the course of the skin score in these patients; however, until the present moment, none of the drugs showed unequivocal effects in the progression of cutaneous involvement. The control of this process reflects a higher survival and a lower morbidity for patients as demonstrated by studies previously performed,\(^4,8\) hence the justification of the excessive search of improvement in these parameters.

Cyclophosphamide (CPM) is an immunosuppressive alkylating agent which suppresses and modulates lymphocytes by means of the modification of cellular components. Basic effects of this drug in patients carrying SSc and pulmonary interstitial fibrosis have been demonstrated with stabilization or even improvement of the evaluated parameters in thorax tomography, bronchoalveolar lavage and respiratory function test, and, as secondary conclusion, an improvement in the analyzed cutaneous parameters was demonstrated.\(^12,13\) Nevertheless, the benefits in patients with exclusive severe cutaneous involvement, that is to say, in patients without pulmonary, renal or cardiac alterations, has not been studied yet, and this was the objective that led the authors to do this study.

Therefore, with the objective of fulfilling this gap in the literature, the purpose of this work is to evaluate the effectiveness of cyclophosphamide used specifically in the treatment of severe cutaneous scenario of patients with systemic sclerosis.

**PATIENTS AND METHODS**

Retrospectively, we selected all the patients with SSc in the diffuse form, without pulmonary involvement, with modified Rodnan score higher than 30 (0-51) and who had indication of cyclophosphamide for the exclusive control of cutaneous fibrosis. Selection period was performed between 2002 and 2007 during the clinical attendance in the Rheumatology service.

All patients fulfilled the ACR classification criteria for diffuse SSc\(^5\) with ages between 18 and 70 years and without history of severe or symptomatic pulmonary involvement, discarded by high resolution thorax tomography (HRT) and pulmonary function test (CVF > 80%). Besides that, patients with a history of previous use of cyclophosphamide, methotrexate, azathioprine and/or corticosteroids in a dosage superior to 30 mg/day and prednisone or equivalent were excluded.

According to the service protocol, the initial dose of CPM administered in the patients was 0.5 g/m\(^2\), with progressive increase up to 1 g/m\(^2\) of body surface, monthly and intravenously, with dose modifications based on the monthly monitoring of the complete hemogram. The progressive increase of the cyclophosphamide dose is performed according to the clinical protocol of the service —, the initial dose is reduced with a later increasing for the patients’ safety, which prevents undesired collateral effects in the beginning of the treatment such as severe leucopenia that could lead to the drug discontinuation.

Besides that, all the patients using this therapy did monthly laboratorial tests such as hemosedimentation velocity, proteins electrophoresis, renal function, hepatic function and urinalysis. The ANF autoantibodies, anticientromere and anti-Scl70 were analyzed in the diagnosis phase of the disease. The skin evaluation based on MRSS was performed each 6 months until the end of the 12 month-therapy and, in some patients who remained under monthly treatment with cyclophosphamide, up to 18 months. The beginning of the disease was considered the first clinical symptom perceived by the patient, and in all cases Raynaud’s phenomenon was reported.

The primary conclusions were a MRSS reduction by comparing values in the beginning of the treatment, at 6 months, at 12 months and in some patients at 18 months of treatment with CPM in the dose already mentioned.

Secondary conclusions were the evaluation of collateral effects, such as: infection, hemorrhagic cystitis and myelosuppression. Prevention of nausea is done with the use of cyclophosphamide, according to the service protocol, with the use of ondansentron 4 to 8 mg during the infusion and dimenhydrinate in the next 24 to 48 h according to the individual need of each patient. The prevention of hemorrhagic cystitis is done by a monthly infusion of 500 mL of physiologic saline solution during the monthly cyclophosphamide infusion allied to oral hydration, mean 2000 mL/day, for 48 hours after the infusion, offered to all patients. Myelosuppression is controlled by the performance of monthly hemograms 5 days before the next infusion for dose adjustment of the administered medication, and for infectious control all patients are oriented to look for our service in the event of indicative signs such as fever, shivers, dyspnea, and dysuria, among others.

**Statistical analysis:** The statistical analysis was performed by the descriptive method of probability of the Friedman’s nonparametric test. P < 0.05 was considered significant.

**RESULTS**

During the period from 2002 to 2007, 21 patients with dSSc had indication of CPM for the exclusive treatment of cutaneous involvement with MRSS (0-51 points) higher than 30 points. Of these 21 patients, 12 were excluded from the
study, six because they had used immunosuppressive drugs previously to the study and six more patients due to the presence of pulmonary fibrosis evidenced in the TCAR. At the end, nine patients remained for the analysis.

From the total of nine patients who fulfilled the inclusion criteria of the study, most of them were female (77%), with age ranging from 19 to 62 years (mean of 41.7 years). Four were Caucasians (45%), three were black (33%) and two, mulattos (22%). The mean time of the disease at the beginning of the therapeutic was 2.22 ± 1.09 years (Table 1).

In relation to the antibodies, we observed that only two patients were positive for antitopoisomerase I and none presented anticentromere.

As to the treatment, seven of the nine patients were treated for 18 months with monthly CPM in the dose established in the methods, because in spite of the initial cutaneous improvement, the thickening remained intense, leading to functional limitations in the patients. The MRSS evaluation was performed in all patients during the treatment period, and the initial values presented a mean of 37.7 ± 4.08 points (variation of 32-47 points).

After six months of treatment we did not observed a significant reduction in the MRSS when compared to the initial values (MRSS ± DP: 37.77 ± 4.08 versus 32.88 ± 7.81; P = 0.58). On the contrary, after 12 months of treatment there was a relevant reduction of the MRSS when compared to the baseline (MRSS ± DP: 37.77 ± 4.08 versus 29.22 ± 8.13; P = 0.009). Analyzing only the group of patients (n = 7) who completed 18 months of treatment, we observed that the MRSS reduction already observed at 12 months of drug use remained significant until the end at 18 months of treatment (mean MRSS 18 months 26.42 ± 10.08; P = 0.01) (Table 2).

The evaluation of the inflammatory activity tests such as serum gamaglobulin, hemosedimentation velocity or serum albumin did not show a significant reduction during the whole treatment (data not shown). However, the dosage of reactive C protein showed a significant reduction if we compare the initial values (mean mg/dL 8.9 ± 10.51) with the values after 18 months of treatment (mean 18 months 3.09 ± 3.48; P = 0.04). Nevertheless, this difference was not observed at the end of 12 months of study (mean mg/dL 12 months 4.61 ± 6.02; P = 0.8).

During the analyzed period infections, hemorrhagic cystitis, microscopic hematuria or myelossuppression which could justify interruption of the treatment were not observed.

**DISCUSSION**

Our study proves for the first time that cyclophosphamide has a beneficial effect specifically in the skin of patients with severe diffuse SSc. We observed that the effect of the drug begins at the end of one year of treatment with stabilization of this cutaneous thickening reduction in up to 18 months. Besides that, there was a decrease in one inflammatory parameter and no severe adverse events, which highlighted the safety of the drug in these patients.

It is known that adequate control of cutaneous manifestation of the disease is associated to a morbidity and mortality reduction, thus demonstrated by Steen and Medsger,4 who

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**Table 1**

Clinical, demographic and laboratorial characteristics and time of treatment of nine patients with diffuse SSc (MRSS > 30)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Beginning of the disease (year)</th>
<th>Time of the disease at the beginning of the therapy (year)</th>
<th>Time of the treatment (months)</th>
<th>Anti-Scl70</th>
<th>Anti-ACA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>56</td>
<td>2003</td>
<td>1</td>
<td>18 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>62</td>
<td>2001</td>
<td>2</td>
<td>18 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>52</td>
<td>1998</td>
<td>3</td>
<td>12 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>19</td>
<td>2001</td>
<td>1</td>
<td>18 months</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>31</td>
<td>2003</td>
<td>3</td>
<td>12 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>54</td>
<td>2001</td>
<td>2</td>
<td>18 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>24</td>
<td>2003</td>
<td>1</td>
<td>18 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>41</td>
<td>2002</td>
<td>3</td>
<td>18 months</td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>37</td>
<td>2001</td>
<td>4</td>
<td>18 months</td>
<td>Pos</td>
<td>Neg</td>
</tr>
</tbody>
</table>

Anti-Scl70 = Antitopoisomerase antibody; Anti-ACA = Anticentromere antibody; Neg = negative; Pos = positive.
concluded in their series of 278 individuals that patients with reduction in at least 25% of the skin scores compared to the initial value presented a 90% survival in 5 years while the ones “nonresponsive” to therapy presented a similar survival rate of 77%. These data were confirmed by the study by Shand et al.\(^8\) in which patients carrying a higher value of MRSS with little reduction during treatment reflected a group of patients with higher mortality.\(^8\)

Various therapies were evaluated with the objective of reducing the progression of the skin score in these patients; however until this moment no drug had unequivocal effects in the progression of the cutaneous involvement. Krishna Su-manth et al.\(^9\) showed that methotrexate 15 mg in a weekly dose is not effective in the treatment of skin scores and pulmonary alterations in the evaluation after 6 months of therapy, although an improvement in the skin scores after 1 year of follow-up have been reported. Pope et al.\(^10\) did not demonstrate a significant improvement of the MRSS even after 1 year of therapy with methotrexate. Azatioprine was evaluated in comparison with cyclophosphamide in the treatment of early dSSc, and the results showed an improvement of the cutaneous and pulmonary parameters only in the group treated with CPM.\(^11\) Nevertheless, none of these studies had as primary target the evaluation of the skin scores in dSSc.

The therapeutical effect of cyclophosphamide in the treatment of SSC has been frequently analyzed in the last decades, especially in pulmonary interstitial disease. However, only recently prospective, randomized, controlled studies were performed which showed an improvement or stabilization of the pulmonary function over one year of treatment.\(^12,13\) The effect of the drug in the cutaneous thickening of the patients was analyzed, but only as a secondary conclusion of these studies.

With the objective of reducing this interference of pulmonary involvement in the study of cyclophosphamide effectiveness in skin thickening of the patients with SSC, M. Calguneri et al.\(^16\) analyzed cutaneous parameters of patients with the early disease in its diffuse form after the use of CPM associated to corticosteroids. The group observed an improvement of the skin only later, after 24 months, but it did not evaluate the thickening objectively using MRSS. Tashkin DP et al.\(^12\) also evaluated the effectiveness of CPM in the treatment of SSC pulmonary fibrosis and, as secondary conclusion, it analyzed the effectiveness of the drug in the cutaneous lesions. The studied population, however, included patients with SSC in its limited and diffuse forms with values of MRSS too variable and mean inferior to 30, cut off established by us to empirically select patients with greater severeness of the cutaneous involvement. The authors observed a beneficial effect in these patients’ skin at the end of 12 months of treatment, with persistence of this effect for up to two years after the use of the drug. Similarly the analysis performed in its series by Valentini et al.\(^13\) demonstrated the beneficial effect of cyclophosphamide in the treatment of cutaneous involvement in patients with early dSSc, with approximate reduction of 30% in the MRSS. As in the study performed by Tashkin DP et al.\(^12\) the initial MRSS mean was inferior to the cut off we established, with variation between 17 and 34, that is to say, including patients with minor cutaneous severeness.

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>INITIAL</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>40</td>
<td>33</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Patient 2</td>
<td>44</td>
<td>43</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Patient 3</td>
<td>32</td>
<td>21</td>
<td>21</td>
<td>*</td>
</tr>
<tr>
<td>Patient 4</td>
<td>38</td>
<td>36</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Patient 5</td>
<td>42</td>
<td>28</td>
<td>22</td>
<td>*</td>
</tr>
<tr>
<td>Patient 6</td>
<td>39</td>
<td>32</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Patient 7</td>
<td>32</td>
<td>28</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Patient 8</td>
<td>36</td>
<td>46</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Patient 9</td>
<td>37</td>
<td>29</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>37.77 ± 4.08</td>
<td>32.88 ± 7.81</td>
<td>29.22 ± 8.13</td>
<td>26.42 ± 10.28</td>
</tr>
<tr>
<td><em>p</em>*</td>
<td>-</td>
<td>0.58</td>
<td>0.009</td>
<td>0.01</td>
</tr>
</tbody>
</table>

SD = Standard deviation. *Patients who did not complete 18 months of treatment. P < 0.05 considered significant. **Always comparative to the initial values.
Additionally, Valentini et al.13 confirmed through the evaluation by HAQ-DI (Health Assessment Questionnaire – Disability Index) the benefits of cyclophosphamide in quality of life improvement and reduction of disabilities of this group of patients, which can be related to the cutaneous and pulmonary improvement observed. Data extracted from the Scleroderma Lung Study also demonstrated a functional and mental improvement as well as of quality of life in patients with dSSc after using oral cyclophosphamide, which the authors associated with the initial improvement of pulmonary, muscle skeletal and cutaneous involvement.17

Till the present moment, we know that the skin severeness of patients with SSc reflects a greater morbidity and mortality, but its involvement does not have linear relation with the involvement of internal organs.8 Proving the therapeutic effectiveness of a treatment specifically for the cutaneous disease could help the rheumatologist and consequently result in the reduction of morbidity and perhaps of mortality of patients with SSc.

Therefore, unlike the previously published studies, our group analyzed the skin of patients with severe diffuse SSc (elevated MRSS) in an objective and constant manner during a minimum period of 12 months, without the interference of factors such as severe pulmonary or cardiac disease. The retrospective view of this study does not reduce its relevance; however prospective and controlled studies may help confirming our results. It should be highlighted that the improvement of the cutaneous score, in our studied population, also occurred in patients with an already established disease and not only in patients with early disease, which would justify the attempt treating patients late after the diagnosis of the disease.

As secondary objectives, we also observed that there was a reduction in one of the inflammatory parameters at the end of 18 months of treatment, reactive C protein, possibly signaling a beneficial and systemic response to the drug. Other important observation was the almost inexistence of adverse effects, proving that the use of intravenous CPM in the monthly treatment of systemic sclerosis is very safe. This datum found in our study is in agreement with literature.18

Our main limitation was the scarce number of patients with severe cutaneous problems, but without onset of other organs such as lung and/or heart. Therefore, we highlight once more that these data should be confirmed by prospective studies and with the inclusion of various clinical centers.

Hence, we conclude that CPM reduced the severe cutaneous thickening in patients with diffuse SSc and could in the future have beneficial effects in morbidity and mortality of the disease.

REFERÊNCIAS

Cyclophosphamide: effective in the treatment of severe SSc

