Myelopathies Secondary to Sjögren's Syndrome: Treatment with Monthly Intravenous Cyclophosphamide Associated with Corticosteroids

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ABSTRACT. ***Objective***. Central nervous system manifestations in Sjögren's syndrome (SS) include focal deficits, optic neuritis, and myelopathies. Acute and chronic myelopathies are frequently severe and sometimes respond poorly to corticosteroids. The efficacy of intravenous (IV) cyclophosphamide (CYC) has been suggested in single case reports.

Methods. We describe the potential usefulness of IV CYC in SS patients with severe myelopathies. Fourteen patients [with acute (n = 6) and chronic (n = 8) myelopathies] were treated with monthly CYC infusions (700 mg/m^2) in addition to 500 mg of corticosteroids for one year. We evaluated the disability before and after CYC treatment using a walking distance calculation and the Expanded Disability Status Scale (EDSS).

Results. CYC treatment was well tolerated in all cases without serious adverse events. Nine patients (including the 6 with acute myelopathy) were improved after CYC treatment. Three patients were stabilized and 2 patients with chronic myelopathies had moderate progression of disability. The mean walking distance increased from 48.2 m before to 180.4 m after CYC treatment ($p < 0.02$). Mean EDSS score decreased from 6.6 to 5.7 (not significant). We found a correlation between the length of time before CYC treatment and clinical improvement for both the walking distance ($p < 0.02$) and the EDSS score ($p < 0.05$).

Conclusion. Although a randomized multicenter controlled study is warranted to confirm our findings, IV CYC infusions seem to be useful for the treatment of myelopathies secondary to SS, particularly in acute but also in progressive cases. This treatment should be strongly considered as soon as possible when disease progression is observed. (J Rheumatol 2006;33:709–11)

Key Indexing Terms:
SJÖGREN'S SYNDROME MYELOPATHY CYCLOPHOSPHAMIDE

Central nervous system manifestations in Sjögren's syndrome (SS) include focal deficits (stroke-like and multiple sclerosis-like episodes), optic neuritis, extrapyramidal syndromes, seizures, and myelopathies[1-3]. Acute and chronic myelopathies are frequently severe and sometimes respond poorly to corticosteroids[3,4]. The few studies reporting drugs such as chlorambucil and azathioprine to be effective in treating myelopathy in SS have been case reports[5,6]. Similarly, despite its potential in treating vasculitis and various autoimmune diseases, intravenous (IV) cyclophosphamide (CYC) has been shown to be effective only in single case reports or in small series of SS patients with neurological manifestations[4,7,8].

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We investigated the outcome of IV CYC treatment in 14 SS patients with severe acute or chronic myelopathies.

MATERIALS AND METHODS

Patients. We retrospectively analyzed a cohort of 82 patients with SS and neurological manifestations[3]. All patients had primary SS as defined by the American–European criteria[9]. No patient had systemic lupus erythematosus or other associated systemic disease. Myelopathies were defined as symmetric motor, sensory, and/or urinary symptoms suggesting medullar involvement and progressing for less than 4 weeks (acute myelopathy) or for more than 6 months (chronic myelopathy). Fourteen patients (6 with acute and 8 with chronic myelopathies) were treated with CYC infusions because of severe disability despite at least 2 courses of IV corticosteroids (1 g/day for 3 days) followed by 6-month treatment with oral corticosteroids alone (1 mg/kg/day for one month), followed by progressive decrease of 5 mg/15 days. The demographic data of the 14 patients are summarized in Table 1.

Methods. All patients were treated for 1 year with monthly IV pulse CYC (700 mg/m^2/mo) in addition to IV methylprednisolone (500 mg), and mesna (600 mg) to prevent cystitis. Patients also received an antiemetic drug (domperidone).

The following clinical data were collected: gender, age, disease duration, objective walking distance, and Expanded Disability Status Scale (EDSS)[10] score at baseline (M0), after 12 months (M12), and at the end of followup. For each patient, EDSS scores were evaluated by the same observer before, during, and after CYC treatment. Biological and immunological screening

Table 1. Demographic and clinical data. Values are mean ± SD unless otherwise stated.

	All SS Patients, n = 14	Acute Myelopathies, n = 6	Chronic Myelopathies, n = 8
Sex ratio: women/men	9/5	4/2	5/3
Age at onset of SS, yrs	53.1 ± 12.6	53.5 ± 10.3	59.5 ± 14.2
Age at start of CYC treatment, yrs	59.5 ± 14.3	57.1 ± 11.2	59.5 ± 14.2
Delay between first neurological symptom and CYC, yrs	2.3 ± 1.2	1.1 ± 0.5	3.1 ± 2.8
Duration of followup after CYC, yrs	2.4 ± 0.8	2.5 ± 0.7	2.3 ± 1
Walking distance at M0, m	48.2 ± 59	5 ± 7.1	80.6 ± 60
Walking distance at M12, m	180.4 ± 183.2*	250 ± 195.8	128.1 ± 53
Walking distance at the end of the followup, m	239.3 ± 178.2*	390 ± 344.1	126.3 ± 155.1
EDSS at M0	6.6 ± 0.84	7.3 ± 4.8	6.1 ± 0.7
EDSS score at M12	5.75 ± 1.3	5.5 ± 1.4	5.8 ± 1.2
EDSS score at the end of the followup	5.9 ± 1.2	5.3 ± 1.7	6 ± 1.3

CYC: cyclophosphamide; EDSS: Expanded Disability Status Scale; SD: standard deviation, M0: month 0 (beginning of CYC treatment), M12: Month 12 (end of CYC treatment). * $p < 0.02$.

included the following variables: complete blood count, erythrocyte sedimentation rate, serum cryoglobulins, total serum gammaglobulins, serum protein immunoelectrophoresis, C-reactive protein, total hemolytic complement and complement factors, antinuclear antibodies, Ro/SSA, La/SSB, RNP, Sm, anti-native DNA, anticardiolipin antibodies, rheumatoid factor, antiprothrombinase, human immunodeficiency virus, and hepatitis B and C serologies. All patients had brain and spinal cord magnetic resonance imaging (MRI) before CYC treatment.

We performed a statistical analysis using paired Wilcoxon tests for numeric value comparisons between baseline and M12 and non-paired Wilcoxon or Pearson tests for other numeric comparisons. We did not perform statistical analysis within these subgroups because of the small sample size.

RESULTS

The demographic and clinical characteristics of our patients with SS are summarized in Table 1. Acute myelopathies were monophasic in 4 cases and recurrent in 2 cases (2 and 3 events, respectively). No patient had antibodies to phospholipids. Six patients (3 with acute and 3 with chronic myelopathies) had circulating cryoglobulin (type III in 2 cases and type II in 4 cases). Complement levels were within normal limits.

CYC treatment was well tolerated in all cases with no serious adverse events. We observed only reversible nausea (n = 3) and leukopenia (n = 2). All patients completed the treatment. Table 1 shows the main results concerning walking distance and EDSS scores. Nine patients (including the 6 with acute myelopathy) showed improvement (EDSS score and walking distance) after CYC treatment. In 4 cases improvement was observed only during the latter half of the treatment between the 6th and 12th infusion. Three patients were stabilized, and 2 patients with chronic myelopathy had a moderate progression of disability. Thus, 12 of the 14 patients (85.7%) were stabilized or improved after CYC treatment. The mean EDSS score decreased from 6.6 ± 0.8 to 5.7 ± 1.3, but the difference did not reach significance. The mean walking distance increased from 48.2 ± 59 meters before to 180.4 ± 183.2 meters after CYC treatment ($p < 0.02$). We found a negative correlation between length of time before CYC treatment and clinical improvement for both walking distance ($r = 0.63$, $p < 0.02$) and EDSS score ($r = 0.56$, $p < 0.05$). The other clinical variables (age and gender) were not correlated with either EDSS or walking distance. After CYC treatment, patients were followed up during a mean of 2.4 ± 0.8 years. The 2 patients with mild progressive disability during CYC treatment continued to progress after CYC and immunosuppressive drugs were stopped. In the remaining 12 patients, one patient (acute myelopathy) died due to an extraneurological event (cardiac infarct). Six patients were treated with azathioprine and 5 patients with mycophenolate mofetil with a sustained stabilization.

Brain MRI was abnormal in 5 cases, showing multiple sclerosis-like lesions in 4 cases and stroke-like lesions in one case. We did not observe gadolinium enhancement on brain MRI. Spinal cord MRI showed a large T2 weighted lesion (more than 2 vertebral levels) in 9 cases and small lesions in 3 cases. Spinal cord MRI was normal in 2 cases (chronic myelopathies). Gadolinium enhancement was observed in 3 cases (all with acute myelopathies).

DISCUSSION

Although a randomized multicenter controlled study is warranted to confirm our findings, monthly intravenous cyclophosphamide infusions seem to be useful for treatment of myelopathies secondary to SS, particularly in acute but also in progressive cases. This result has been reported in single cases but, to our knowledge, our study is the largest on SS myelopathies treated with CYC[4,7]. In our study the treatment was not begun early, since patients first had to have failed corticosteroid monotherapy.

In 4 cases improvement was observed only during the second half of treatment, suggesting the need for prolonged treatment. Similar results have also been observed with myelopathies associated with systemic lupus erythematosus, where CYC is now considered as a first-line therapy if a severe deficit is observed[8].

Because we observed a negative correlation between length of time before treatment and its efficacy, we recommend introducing CYC infusions as soon as possible when disease progression is observed. CYC is probably more effective for cases that are still in an inflammatory phase as demonstrated by its greater efficacy in acute compared with progressive myelopathies. However, the stabilization observed in 6 of the 8 patients with chronic progression before CYC treatment (at least 1 point of EDSS) suggests that it should be considered a success.

In our protocol, in accordance with previous therapeutic trials with CYC, we added 1 g of IV corticosteroids. We cannot therefore rule out the possibility that the corticosteroid may have influenced the improvement of neurological symptoms. However, all our patients had already undergone treatment with IV corticosteroids without any longterm positive effects prior to starting CYC treatment. In our cohort, one point of interest is the sustained therapeutic effect with a mean followup of 2.4 years after ending CYC treatment. CYC therapy stabilized the patients, who did not relapse during followup taking azathioprine or mycophenolate mofetil.

We suggest that a combination of pulse CYC and IV corticosteroids should be strongly considered in patients with SS and acute or chronic myelopathy, and that treatment initiated early in the disease course may be most beneficial.

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