Combination of cyclophosphamide and interferon-β halts progression in patients with rapidly transitional multiple sclerosis

F Patti, M L Cataldi, F Nicoletti, E Reggio, A Nicoletti, A Reggio

Abstract
The effects of combined treatment with cyclophosphamide (CTX) and interferon-β (IFN-β) are described in selected patients with “rapidly transitional” multiple sclerosis. This form of multiple sclerosis is extremely active with very frequent and severe attacks which produce a dramatic increase on the expanded disability status scale (EDSS). Ten patients with rapidly transitional multiple sclerosis were previously treated with interferon-β, but none benefited by this treatment. Monthly treatment with intravenous CTX, from 500 mg/m² to 1500 mg/m² to obtain a chronic lymphocytopenia (600/mm³ to 900/mm³) produced a marked and significant reduction in the number of relapses (p<0.0001), disability previously accumulated (p<0.0001), and a reduction of T2 MRI burden of lesion. This particular group of patients benefited by combining cyclophosphamide and IFN-β. The possibility is considered of carrying out further studies to test the efficacy of the association between the two drugs for patients who are not responsive to IFN-β or other active disease modifying therapies.

Keywords: multiple sclerosis; interferon-β; cyclophosphamide

Several studies have shown that IFN-β and glatiramer acetate are active drugs able to modify the disease course of multiple sclerosis, with a global 30% decrease in the relapse rate in treated patients compared with placebo. Based on the limited clinical efficacy of both IFN-β and glatiramer acetate other drugs have been proposed for experimental treatment in multiple sclerosis (mitoxantrone, azathioprine, fusidate, etc). Combination therapy could improve the control of the disease process.

Patients and methods
We selected 10 patients (six women and four men) affected by clinically definite rapidly transitional multiple sclerosis. The mean age was 24.9 (range 20–28), onset age 21.3 (range 17–24), and mean duration of disease 3.6 years (range 3–5). Relapses occurred in all patients with high frequency and the remission time from each relapse was not easily detectable because of the marked and rapid accumulation of disability. Rarely, a short phase of apparent clinical stability was evident between the succeeding relapses. In our patients a relapse was detected when a new symptom lasting more than 24 hours and causing handicapped sequelae occurred. All of these patients had started to receive IFN-β (six with Avonex and four with Betaseron) within 1 year of the diagnosis of the disease. At the run in mean EDSS was 4.8 and the mean MRI total burden of the
**Table 1 Clinical findings and results**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age</th>
<th>Age at onset</th>
<th>EDSS/months Pre-IFN</th>
<th>EDSS/months IFN</th>
<th>EDSS/months IFN+CTX</th>
<th>Relapse rate in IFN</th>
<th>MRI pre-IFN</th>
<th>MRI IFN</th>
<th>MRI IFN+CTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/24</td>
<td>21</td>
<td>A 3.0/11</td>
<td>4.5/13</td>
<td>2.5/18</td>
<td>3/0</td>
<td>41 (23)</td>
<td>67 (38)</td>
<td>55 (33)</td>
</tr>
<tr>
<td>2</td>
<td>F/23</td>
<td>20</td>
<td>A 2.5/12</td>
<td>4.0/13</td>
<td>2.0/18</td>
<td>4/0</td>
<td>23 (9)</td>
<td>49 (21)</td>
<td>41 (18)</td>
</tr>
<tr>
<td>3</td>
<td>M/26</td>
<td>23</td>
<td>A 3.0/12</td>
<td>5.5/13</td>
<td>2.5/18</td>
<td>4/0</td>
<td>25 (14)</td>
<td>53 (29)</td>
<td>34 (19)</td>
</tr>
<tr>
<td>4</td>
<td>F/20</td>
<td>17</td>
<td>A 2.5/09</td>
<td>4.0/12</td>
<td>1.5/18</td>
<td>5/1</td>
<td>20 (18)</td>
<td>46 (27)</td>
<td>38 (25)</td>
</tr>
<tr>
<td>5</td>
<td>F/28</td>
<td>24</td>
<td>A 2.5/12</td>
<td>4.0/14</td>
<td>1.5/18</td>
<td>3/0</td>
<td>16 (10)</td>
<td>39 (17)</td>
<td>24 (13)</td>
</tr>
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<td>24</td>
<td>A 3.0/11</td>
<td>5.0/12</td>
<td>2.5/18</td>
<td>5/0</td>
<td>43 (18)</td>
<td>70 (36)</td>
<td>48 (27)</td>
</tr>
<tr>
<td>7</td>
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<td>23</td>
<td>B 3.5/12</td>
<td>4.5/13</td>
<td>2.0/18</td>
<td>3/0</td>
<td>52 (21)</td>
<td>78 (35)</td>
<td>59 (26)</td>
</tr>
<tr>
<td>8</td>
<td>F/22</td>
<td>19</td>
<td>B 3.5/12</td>
<td>5.0/12</td>
<td>2.0/18</td>
<td>5/1</td>
<td>35 (15)</td>
<td>61 (28)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>9</td>
<td>M/26</td>
<td>21</td>
<td>B 3.5/12</td>
<td>5.5/16</td>
<td>2.5/18</td>
<td>4/0</td>
<td>31 (16)</td>
<td>47 (26)</td>
<td>37 (22)</td>
</tr>
<tr>
<td>10</td>
<td>F/26</td>
<td>21</td>
<td>B 3.0/12</td>
<td>6.0/15</td>
<td>3.0/19</td>
<td>4/0</td>
<td>23 (12)</td>
<td>50 (24)</td>
<td>32 (16)</td>
</tr>
<tr>
<td>Mean</td>
<td>F-4 M/24.9</td>
<td>21.3 (2.26)</td>
<td>(0.40)/11.4</td>
<td>(0.71)/13.3</td>
<td>(0.48)/18***</td>
<td>(0.82)/0.2***</td>
<td>(2.60)/16.6</td>
<td>(0.82)/0.2***</td>
<td>(0.90)/16.6**</td>
</tr>
</tbody>
</table>

**SD** (2.55)

**p<0.001; ***p<0.0001 (ANOVA). A=Avonex; B=Betaferon; PR=progress rate.**

lesion was 56 cm² (obtained with the Ormerod method). The relapse rate was 4 during the early phase and 4 during the prestudy time (IFN period).

Progression rate of the disease was calculated: it was 0.8 during the pre-IFN period and of 1.6 during the IFN period, suggesting a poor response to IFN-β treatment. All of the relapses were treated with methylprednisolone (1 g/day intravenously for 6 consecutive days followed by a rapid 5 day oral prednisone taper (table 1).

**EXCLUSION CRITERIA**

Exclusion criteria were (1) concomitant diseases (liver, renal, lung, cardiac failures); (2) infectious and blood diseases; (3) other neurological or psychiatric diseases; (4) pregnancy.

**CLINICAL EXAMINATION**

All patients underwent a complete physical examination every month. Determination of the EDSS with the support of functional systems scores (FSS) was performed by a senior neurologist. Blood and urine samples were collected and analysed every day during CTX administration and then every week for the 18 months of treatment. All patients had radiography of the chest at the beginning of the study and every 6 months during the study period.

Brain MRI was obtained by each patient at the end of treatment (data not shown). A further clinical evaluation (FSS and EDSS determination) was performed 1 year after the end of this study. The EDSS was stable in all patients and relapses occurred with very low frequency (two events in the whole group). Only one of the two relapses needed CTX associated treatment.

**THERAPY**

The CTX was intravenously administered from a dose of 500 mg/m² to 1500 mg/m² within 3 consecutive days on a monthly basis for 12 consecutive months so as to obtain a chronic reduction of lymphocytes (600 mm³ to 900/ mm³). At the end of the first year of treatment CTX was administered every 60 days for a further 6 months (at months 14, 16, and 18). Ondansetron was administered intravenously to all patients at a dose of 8 mg/day just before CTX administration. Large volumes of fluids were administered intravenously on the day of treatment.

In association with CTX, all patients continued to receive regular treatment. IFN-β —that is, Avonex at a dose of 6 MIU once a week (intramuscularly injected) or Betaferon at a dose of 8 MIU every other day (subcutaneously injected). Side effects were often occurred; however, with lower frequency compared with previous reports.

**STATISTICAL ANALYSIS**

Analysis of variance (ANOVA) was performed for the analysis of EDSS, relapse rate and T2 MRI burden of lesion changes which occurred after CTX and IFN-β therapy. Pearson’s test was performed to correlate EDSS and MRI burden of lesion.

**ETHICS**

All patients were fully informed on the possible risks deriving from the association between IFN-β and CTX. All of them gave their informed signed written consent before starting CTX associated treatment.

**RESULTS**

During the study period a marked decrease of the relapse number (mean 0.2 (p<0.0001)) and a significant reduction of EDSS, with a mean value of 2.2 (p<0.0001), were found. Also T2 MRI burden of lesion significantly decreased (table 1). A marked reduction in lesion number on T2 images as well as a clear reduction of the lesion area occurred in five of 10 patients.

No significant correlation was found between EDSS and MRI burden of lesion at the end of treatment (data not shown).

At the end of the study all patients continued treatment with only IFN-β (either Betaferon or Avonex). A further clinical evaluation (FSS and EDSS determination) was performed 1 year after the end of this study. The EDSS was stable in all patients and relapses occurred with very low frequency (two events in the whole group).

**SIDE EFFECTS**

In the first months of treatment side effects were rare and mild. Leukopenia and nausea often occurred; however, with lower frequency compared with previous reports. In only one
The clinical improvement noted with the reduction of EDSS could indirectly account for the marked depression of white matter inflammation and T2 signal changes from irreversible damage which otherwise would be present in these patients. Spontaneous restorative processes could occur with higher frequency in these patients.

The association of IFN-β with CTX seemed safe, although previous studies showed that both drugs may produce many side effects.

Conclusions
This study, despite the limits of the design (not blinded and without controls, no previous CTX association) and of the limited sample number, suggests the utility of associating CTX with IFN-β in accurately selected patients who exhibit a rapid and severe worsening of their disability. This association could be maintained for brief period. Our results demonstrate that IFN-β treatment may contribute to the reduction in disease worsening also after the discontinuation of CTX boosters.

We think that the correct selection of patients represents the main point of this pilot observational study.

In conclusion, within its limits, suggests that in patients with rapidly worsening multiple sclerosis, not responsive to the best common therapies, the association of CTX plus IFN-β is amenable, safe, and to be recommended.

Discussion
This study shows that a combination of CTX and IFN-β is able to halt the progression of disability and reduce MRI burden of lesion in “rapidly transitional” multiple sclerosis. McAlpine had previously described a different form of transitional multiple sclerosis.6 He reported a progressive course of multiple sclerosis after one isolated bout. Weistock-Guttman et al defined the “rapidly transitional” form of multiple sclerosis.7 Our patients presented clinical features similar to those described by these authors.

Several lines of evidence show that the association between CTX and IFN-β might improve the clinical profile of patients with rapidly transitional multiple sclerosis. Benefits from the association between these two drugs may depend on the effects of both drugs on the immune system. The reduction of lesion number and burden of lesion (table 1) may indicate a remyelination process. However no significant correlation was found between EDSS and MRI results.

Treatment with CTX reduces both blood and CSF T lymphocytes (changing the CD4/CD8 ratio).3 It induces a shift of T1 lymphocytes towards T2 lymphocytes,10 11 reducing the proinflammatory cytokines (interleukin (IL)-1), IL2, IFN-γ, and IL1210 11 and increasing the anti-inflammatory cytokines (IL4, TGF-β, IL6, and IL10).10–11 All of these modifications returned slowly to normal values a few months after the interruption of CTX administration.13 On the contrary, other evidence showed that the effects of CTX may last a few years after withdrawal9 14.

It has recently been shown that CTX administration is able to slow progression of disability and reduce the accumulating burden of disease.15 These results become more evident when CTX is given to younger patients with a short duration of disease.15 17

We hypothesise that rapidly transitional multiple sclerosis might be due to an overactivation of some lymphocyte clones, mainly active in pathological processes of central white matter. The chronic reduction of T lymphocytes to around 600/mm3 could reduce the proinflammatory activation of cells and cytokines which are increased in this specific form of disease.

The clinical effects of decrease with time (benefits are uncertain after 18 months),18 although previous results obtained in patients with chronic progressive multiple sclerosis showed that the positive effects of the treatment were still detectable after 3 years.14

In our study, combining therapy for a period of 18 months brings the positive effects of this treatment up to 30 months.

15. Gobbiini MI, Smith ME, Richert ND, et al. Effect on open label pulse cyclophosphamide therapy on MRI measures of...

NEUROLOGICAL STAMP

Willem Einthoven (1860–1927)

Einthoven’s lifetime work was dedicated to electrocardiography and its extended applications. He qualified in 1885, and in the same year was appointed professor of physiology at Leiden where he worked until his death. For his development of the electrocardiogram he was awarded the 1924 Nobel Prize for physiology or medicine.

He entered the University of Utrecht in 1878, planning to specialise in ophthalmology and to follow his father into the army and colonial medical services. At Utrecht at the Gasthuis voor Doglijders, a famous eye hospital, he worked with FC Donders, a pioneer of ophthalmology, and also with the ophthalmologist H Snellen.

He wrote two papers as a student. The first was Some remarks on the elbow joint. This was a consequence of his fracturing his own wrist during a gymnastic exercise and was a study of pronation and supination of the arm. In the paper he analysed the anatomy of the arm according to the principles of mathematics and physics. His second paper Stereoscopy by means of colour variation arose from the work for his thesis.

In the late 1880s he performed studies in asthma demonstrating its basis in bronchial spasm which he produced by stimulation of the vagal nerve with carbon dioxide. In 1883 he continued his studies in optics and recorded electrical potentials of the eye and later of the heart. In 1903 he constructed a string galvanometer with which he also recorded the reaction of the eye to light and electrical activity of vagal nerves. In his last experiment in 1927 he recorded the action potential of the sympathetic nerve.

The question was raised whether an instrument (his string galvanometer) should be honoured by a Nobel Prize in physiology or medicine, or physics. The decision to physiology or medicine was agreed after Einthoven’s clarification that the galvanometer was fundamental to the recording of the electrocardiogram, and the clinical application produced very practical results.

Einthoven was honoured philatelically by Mexico in 1972 alongside an American cardiologist Dr Frank Wilson. The stamp also shows a mural by Diego Rivera. As well as Drs Wilson and Einthoven, the heads of Dr James Herrick (left bottom) and Dr Paul Dudley White (right bottom) are shown (Stanley Gibbons 1242, Scott C395).

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