RESEARCH LETTER

Lack of Response to Pulse Cyclophosphamide in Neuromyelitis Optica: Evaluation of 7 Patients

The effect of immunosuppression with corticosteroids, azathioprine, mycophenolate, or rituximab for preventing relapses in patients with neuromyelitis optica (NMO) has been demonstrated in case series and retrospective studies.1-4 These drugs are currently considered the mainstay treatment for preventing neurologic worsening in NMO.5 Herein, we describe our experience with pulse cyclophosphamide for treating patients with NMO, which was used prior to azathioprine and had its use interrupted owing to lack of efficacy.

Methods. We reviewed our previously reported series of patients with relapsing NMO followed up from February 1994 to August 2007 at the Federal University of São Paulo for those treated with intravenous cyclophosphamide for a thorough analysis of this drug’s effect in preventing relapses and disability accumulation in patients with NMO. Inclusion criteria and data analysis are identical to those previously reported.5

Results. We identified 7 patients who received cyclophosphamide in pulse doses of 1 g associated with methylprednisolone, 1 g every 2 months (500-700 mg/m², according to each patient’s body surface area) as a first-line treatment, within a mean of 17 months from the first demyelinating event (optic neuritis, myelitis, or both) (Table). During cyclophosphamide therapy, 5 patients continued relapsing and/or worsening, 1 patient died owing to a severe NMO relapse, and 1 abandoned follow-up at our center (Table); only 1 patient remained clinically stable. The remaining 5 patients on follow-up were switched to azathioprine associated with prednisone after clinical judgment of cyclophosphamide inefficiency. After treatment modification, there was a decrease in annualized relapse rate and/or progression index, with some patients showing improvement in their Expanded Disability Status Scale scores (Table). Patient 1 further showed an increase in annualized relapse rate and received rescue therapy with intravenous immunoglobulin every 2 months.

Comment. Neuromyelitis optica is an autoimmune demyelinating disease of the central nervous system characterized by severe relapses of optic neuritis and myelitis, which are the main factors associated with neurologic disability.6 Therefore, preventing relapses should be the main goal of treatments prescribed for patients with NMO.

In this series of Brazilian patients with relapsing NMO followed up at Federal University of São Paulo, treatment with cyclophosphamide was not able to halt relapses or neurologic disability progression, even being an immunosuppressant with similar mechanism of action to azathioprine (both broadly block DNA and RNA synthesis). Although some relapses were also observed in patients after switching to azathioprine, they were less severe, suggesting that less nervous tissue damage might have occurred, thus allowing better neurologic recovery. The association of NMO-IgG positivity and treatment response could not be established for these patients as this biomarker was only made available in Brazil.

Table. ARR and PI of Patients Taking Cyclophosphamide and Azathioprine

<table>
<thead>
<tr>
<th>Subject, No.</th>
<th>Duration of Treatment, mo</th>
<th>Cumulative Dose, g</th>
<th>ARRA</th>
<th>PI b</th>
<th>Mean Lymphocyte Count</th>
<th>Duration of Treatment, mo</th>
<th>ARRA</th>
<th>PI b</th>
<th>NMO-IgG d</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>6</td>
<td>0.8</td>
<td>0</td>
<td>819</td>
<td>33</td>
<td>3.2</td>
<td>0.5</td>
<td>1</td>
<td>Rescue therapy with intravenous IgG</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>5</td>
<td>3.9</td>
<td>5.9</td>
<td>541</td>
<td>44</td>
<td>0.5</td>
<td>−0.4</td>
<td>0</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>1390</td>
<td>41</td>
<td>0.6</td>
<td>0</td>
<td>NA e</td>
<td>NA e</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0.2</td>
<td>2.9</td>
<td>744</td>
<td>47</td>
<td>0.8</td>
<td>−0.3</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>3</td>
<td>5.0</td>
<td>7.6</td>
<td>940</td>
<td>43</td>
<td>0</td>
<td>−0.1</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>5</td>
<td>2.0</td>
<td>4.5</td>
<td>NA f</td>
<td>44</td>
<td>0</td>
<td>−0.1</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>3</td>
<td>3.0</td>
<td>8.3</td>
<td>745</td>
<td>41.6 (4.9)</td>
<td>1.0 (1.3)</td>
<td>−0.1 (0.4)</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Mean (SD) 9.8 (3.5) 4.0 (1.4) 2.1 (2.0) 4.2 (3.4) 863.0 (289.0) 41.6 (4.9) 1.0 (1.3) −0.1 (0.4)

Abbreviations: AE, adverse event; ARR, annualized relapse rate; NA, not available; NMO, neuromyelitis optica; PI, progression index.

**A** Calculated as the total number of relapses divided by disease duration (in years).

**B** Calculated as Expanded Disability Status Scale score during a patient’s last doctor visit divided by disease duration.

**C** Information retrieved from complete blood count examinations recorded in the hospital while patient was receiving cyclophosphamide treatment.

**D** Includes anti-aquaporin-4 antibodies.

**E** NMO-IgG was only made available in Brazil after 2007, thus patients seen before 2007 could not have been tested, and all samples from these series were obtained from patients under treatment.

**F** This patient performed complete blood count examinations in an external laboratory, but information could not be retrieved.
after 2007 and the relationship between this antibody titer, disease severity, and treatment response is still under research.3
The reason for cyclophosphamide treatment failure could not be identified solely on clinical information, and we speculate that it might have occurred owing to the doses we used or dosing interval—even though 5 patients presented with a lymphocyte count below 1.000/µL (to convert to \( \times 10^9 \) per liter, multiply by 0.001) while taking the therapy—which would be better understood in an experimental setting. Nevertheless, considering the known response of azathioprine,1 mycophenolate,3 and rituximab,2 the results presented here should discourage the use of cyclophosphamide in pulse doses for the treatment of NMO.

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Author Contributions: Dr Bichuetti had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bichuetti and Oliveira. Acquisition of data: Bichuetti and de Castro Boulos. Analysis and interpretation of data: Bichuetti, de Castro Boulos, and Gabbai. Drafting of the manuscript: Bichuetti and de Castro Boulos. Critical revision of the manuscript for important intellectual content: Oliveira and Gabbai. Statistical analysis: Bichuetti. Administrative, technical, and material support: de Castro Boulos. Study supervision: Oliveira and Gabbai.

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COMMENTS AND OPINIONS

IDEAL for CCSV1 Research

Read with great interest the editorial titled “No Endovascular Innovation Without Evaluation in Chronic Cerebrospinal Venous Insufficiency: A Call for the IDEAL Model” by Williams and Venkatesan.1 Although I very much support the IDEAL model to prevent uncontrolled dissemination of unproven or even harmful procedures, this does not mean that any sort of research can be done. The authors stated that the demand by patients with multiple sclerosis for research on endovascular interventions in chronic cerebrospinal venous insufficiency (CCSV1) is so great that any call to halt it would serve only to propel the unregulated and unmonitored off-label practice, which is likely to cause more harm than would carefully monitored clinical trials. What this actually means is that you have to tell your patient during informed consent, when you perform research for CCSVI, that you do this to prevent further unregulated off-label use, which is likely to cause harm. In article 9 of the Declaration of Helsinki, it is stated: “Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights.” Asking patients to participate in a trial just to prevent unregulated and unmonitored off-label practice means that the researcher does not believe the CCSVI hypothesis is true. The overwhelming accumulation of high-quality papers all speaking against CCSVI in the last 2 years, some published in this journal, actually make it impossible to believe that the CCSVI hypothesis is or can be true. Medical research should only be conducted to find an answer to a research question, not to satisfy the popular voice. The original IDEAL paper also stated: “Trials are unnecessary when an advance is clear and substantial.”2 I would argue that the opposite is also true: Trials are also unnecessary when the advance is clearly unproven. Research should be conducted to challenge scientific doubt and when there is no scientific doubt, either positive or negative, any trial is unethical and should not be performed.

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