Cyclosporine in the treatment of severe attack of ulcerative colitis: a systematic review

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ABSTRACT

Introduction: Intravenous steroid therapy is the standard treatment in severe attacks of ulcerative colitis (UC), but 20% to 60% of patients fail to respond and require colectomy. Cyclosporine (CyA) has shown efficacy in steroid failures and could avoid surgery, but controversy remains.

Methods: We did a systematic review using Cochrane methodology, including data from published (in English, French, Spanish or German) clinical trials done in adults using intravenous or oral CyA in UC. Data on efficacy are obtained from controlled and observational clinical trials, and for safety issues case reports are also considered.

Results: 31 studies were identified which met the inclusion criteria, 22 (18 uncontrolled, 4 controlled) with intravenous CyA, and 9 (all uncontrolled) using oral CyA. Only 4 controlled trials (one in abstract form) are available, and only one compares CyA to placebo. However, efficacy results are very consistent in these 4 trials, and very similar to those in observational studies. CyA achieves remission in 91.4% and 71.4% of patients in controlled and uncontrolled studies using intravenous route, and in 71.2% using oral route. Two mg/kg/day seems so efficacious and safer as previous standard 4 mg/kg/day dose. Minor side effects are rather common but do not seriously limit therapy. Severe side effects, specially infections, are uncommon but clinically relevant with several deaths reported.

Conclusion: CyA (intravenous, 2 mg/kg/day) constitutes an efficacious and relatively safe alternative in the treatment of severe, steroid-refractory, attack of UC. To optimize treatment, the correct selection of patients, a standardized protocol and clinical surveillance are recommended.

CICLOSPORINA EN EL TRATAMIENTO DE LOS EPISODIOS GRAVES DE COLITIS ULCEROSA: UNA REVISIÓN SISTÉMATICA

Introducción: La administración intravenosa de esteroides es el tratamiento habitual en los episodios graves de colitis ulcerosa (CU), aunque el 20-60% de los pacientes no respon- den a él y precisa intervención quirúrgica mediante colectomía. La ciclosporina (CyA) ha demostrado ser eficaz en los cuadros de falta de respuesta a los esteroides y podría evitar la intervención quirúrgica; no obstante, existe controversia a este respecto.

Objetivo: El objetivo del presente estudio ha sido efectuar una revisión sistemática con objeto de evaluar la eficacia y seguridad de la CyA para conseguir la remisión en pacientes con un episodio grave de CU.

Métodos: Revisión sistemática mediante la metodología Cochrane, incluyendo los datos correspondientes a los ensayos clínicos publicados en inglés, francés, español o alemán, y referidos a pacientes adultos con CU tratados mediante la administración intravenosa u oral de CyA. Los datos de eficacia se obtuvieron a partir de los ensayos clínicos efectuados con controles y de los estudios de observación; también se consideraron los casos aislados respecto a las cuestiones de seguridad.

Resultados: Se identificaron 31 estudios que cumplan los criterios de inclusión en la revisión, 22 (18 sin control y 4 con control) en los que se administró CyA intravenosa y 9 (todos ellos sin grupo control) en los que se administró CyA por vía oral. Sólo se hallaron 4 ensayos clínicos realizados con controles (uno de ellos publicado en forma de resumen), y en sólo uno de ellos se comparó la CyA con placebo. No obstante, los resultados de eficacia fueron muy similares en los 4 ensayos clínicos y también en los estudios de observación. En los estudios realizados con y sin controles, la CyA intravenosa dio lugar a remisión en el 91.4 y el 71.4% de los pacientes, respectivamente, mientras que el porcentaje co-
GARCÍA-LÓPEZ S, ET AL. CYCLOSPORINE IN THE TREATMENT OF SEVERE ATTACK OF ULCERATIVE COLITIS: A SYSTEMATIC REVIEW

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease that usually alternates phases of clinical activity, usually known as «flare-ups» or attack, with phases of clinical remission. This intermittent course is the most common in the natural history of UC: in fact 90% of patients show this pattern if the follow-up is long enough. About 15% of patients suffer in a given moment from a severe attack, a clinical situation which had 30% to 50% mortality in the pre-steroid era.

In 1954 and 1955 the Oxford Group published in 2 parts a key clinical trial in the British Medical Journal. It was a randomized, controlled, and blind study that demonstrated that hydrocortisone is clearly superior to placebo in the treatment of attacks or UC. Although ultimately between 30% and 50% of patients required surgical treatment, hydrocortisone was clearly superior to placebo both in moderate and severe cases, and the mortality rate fell to roughly 5%. Ten years later, Truelove and Jewell published another key observational study: a fixed day for colectomy in steroid failures by protocol situated the final mortality in a standard rather difficult to improve: 1%. This strategy was adopted around the world, with some local variations (5 to 14 days of steroid treatment before colectomy).

Steroids are far from perfect treatment, however. Besides common and significant side effects, colectomy is still strongly indicated in steroid failures by protocol situated the final mortality in a standard rather difficult to improve: 1%. This strategy was adopted around the world, with some local variations (5 to 14 days of steroid treatment before colectomy).

Efficacy

The first aspect we need to highlight is that there was considerable heterogeneity among the different studies. Most papers evaluated the efficacy of CyA in patients with severe attacks of UC that were considered refractory to steroids. However, the definitions of «refractory» or «severe» were not uniform, and the doses of steroids, the accompanying therapy (for example, with antibiotics or parenteral nutrition) and, above all, the duration of the previous treatment and definitions of response were highly variable. CyA was administered by the topical (rectal) route.

RESULTS

We assessed the data from studies that had used CyA via the oral route separately from those using intra-venous administration. This was for 3 reasons: a) it is possible that the effect of the drug would be slightly different when it is administered by the oral route and when it is administered intra-venously, especially considering that CyA is metabolized and eliminated in different ways for each route; b) the doses are difficult to equate even with the new neo-oral formulations; and c) an assumption that, generally, the oral route is employed in patients with less severity of the disease. We tabulated the data and expressed the percentage and the 95% confidence intervals (95%CI), as well as the weighted mean (to adjust for the number of patients included in each study).

METHODS

In searching the literature we used the key words «cyclosporine» («Cy-closporine» [MESH] and «ulcerative colitis» («Colitis, ulcerative/The- ray» [MESH]) in the MEDLINE database, accessed via the search engine PubMed. Using the same key words we reviewed the Cochrane Central Register of Controlled Trials. The search was conducted up to July 2004 and all papers in English, French, Spanish or German were included. From the articles obtained we evaluated the references cited, selecting those that were potentially relevant. Further, we reviewed the summaries of the last 10 years of the DDW (Digestive Disease Week) and of the UEGW (United European Gastroenterology Week). To evaluate the efficacy of the drug, we considered data derived from clinical trials and of the observational series, whether prospective or retrospective. When reviewing safety we did also consider reports of individual cases, because infrequent side-effects can be overlooked in these series of patients.

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We treated the data in terms of response to some basic clinical questions in the setting of acute severe attack of UC: is really CyA efficacious in the treatment of acute attacks of UC?, is it a safe alternative in this context?, at what dose and by which route should it be administered?

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In searching the literature we used the key words «cyclosporine» («Cy-closporine» [MESH] and «ulcerative colitis» («Colitis, ulcerative/The- ray» [MESH]) in the MEDLINE database, accessed via the search engine PubMed. Using the same key words we reviewed the Cochrane Central Register of Controlled Trials. The search was conducted up to July 2004 and all papers in English, French, Spanish or German were included. From the articles obtained we evaluated the references cited, selecting those that were potentially relevant. Further, we reviewed the summaries of the last 10 years of the DDW (Digestive Disease Week) and of the UEGW (United European Gastroenterology Week). To evaluate the efficacy of the drug, we considered data derived from clinical trials and of the observational series, whether prospective or retrospective. When reviewing safety we did also consider reports of individual cases, because infrequent side-effects can be overlooked in these series of patients.

RESULTS

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The first aspect we need to highlight is that there was considerable heterogeneity among the different studies. Most papers evaluated the efficacy of CyA in patients with severe attacks of UC that were considered refractory to steroids. However, the definitions of «refractory» or «severe» were not uniform, and the doses of steroids, the accompanying therapy (for example, with antibiotics or parenteral nutrition) and, above all, the duration of the previous treatment and definitions of response were highly variable. CyA was administered by the intra-venous route in the majority of studies, while sometimes the oral route was used. Methodologically, the majority of the studies were observational series or non-con-
trolled clinical trials; only 4 of the published studies, all using the intravenous route of administration, were controlled trials\(^ {26-29}\), including one that had been published only as an abstract\(^ {29}\).

**TREATMENT WITH INTRAVENOUS CYCLOSPORINE**

**Non-controlled studies**

Table I summarizes the 18 non-controlled studies\(^ {8-25}\) using intravenous CyA which had been published at the time of our analysis. The majority had been conducted in patients with severe attacks of UC refractory to intravenous steroids, but some studies included moderate cases, and the dose and time of steroid administration were highly variable, as previously stated. Any case, the total number of patients included was 491, a very important figure when comparing with controlled trials. The median initial dose used was 3.9 mg/kg/day (range: 2-5). There is no obvious relationship between dose and response as some large trials using 2 mg/kg dose show the same mean rate of response. The mean time of response, which was clearly specified only in 8 studies varied between 5.8-16 days. The rate of overall response, defined in several different ways but most frequently as the rate to avoid colectomies, was 71.4% (95% CI, 0.67-0.75), which means in real numbers avoiding colectomy in 351 of the 491 patients.

**Controlled studies**

There were 4 controlled studies using intravenous CyA in the treatment of severe UC attack, 3 of them complete reports and the 4th as a summary\(^ {26-29}\). Of the 3 complete reports published, one evaluated the efficacy of CyA in patients with severe attack of UC without response to corticoids compared to a group on placebo, the steroids being maintained in both groups\(^ {28}\). The second study evaluated the efficacy of CyA in mono-therapy as compared with mono-therapy with steroids\(^ {27}\). The third study compared the efficacy of intravenous administration of 4 mg/kg against a dose of 2 mg/kg\(^ {28}\). The study published as a summary compared mono-therapy CyA against its combination with steroids\(^ {29}\). Table II summarizes the most important data from these studies. Overall, taking

### Table I. Non-controlled studies using intravenous cyclosporine in the treatment of severe attack of ulcerative colitis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Initial dose (mg/kg/day)</th>
<th>Patients (n)</th>
<th>Responders (%)</th>
<th>Response time (days)</th>
<th>Left-side colitis (patients, n)</th>
<th>Extensive colitis (patients, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCormack et al(^ {2})</td>
<td>4</td>
<td>46</td>
<td>32 (69)</td>
<td>–</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Rolny et al(^ {9})</td>
<td>4</td>
<td>19</td>
<td>14 (73)</td>
<td>16</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Salsali et al(^ {10})</td>
<td>5</td>
<td>32</td>
<td>20 (62)</td>
<td>7.5</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Rowe et al(^ {11})</td>
<td>2</td>
<td>36</td>
<td>23 (69)</td>
<td>–</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Haslam et al(^ {12})</td>
<td>4</td>
<td>26</td>
<td>16 (69)</td>
<td>–</td>
<td>16</td>
<td>–</td>
</tr>
<tr>
<td>Hermida-Rodríguez et al(^ {13})</td>
<td>4</td>
<td>15</td>
<td>10 (66)</td>
<td>8</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Gründke et al(^ {14})</td>
<td>4</td>
<td>7</td>
<td>6 (85)</td>
<td>9</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cohen et al(^ {15})</td>
<td>4</td>
<td>42</td>
<td>36 (85)</td>
<td>–</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Aria et al(^ {16})</td>
<td>2</td>
<td>40</td>
<td>26 (65)</td>
<td>–</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Stack et al(^ {17})</td>
<td>4</td>
<td>22</td>
<td>20 (90)</td>
<td>–</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Hyde et al(^ {18})</td>
<td>4</td>
<td>30</td>
<td>24 (80)</td>
<td>–</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Wenzel et al(^ {19})</td>
<td>4</td>
<td>16</td>
<td>11 (73)</td>
<td>7</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Van Gouwn et al(^ {20})</td>
<td>4</td>
<td>29</td>
<td>20 (69)</td>
<td>–</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>Carbonnel et al(^ {21})</td>
<td>4</td>
<td>32</td>
<td>20 (62)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Suntar et al(^ {22})</td>
<td>5</td>
<td>21</td>
<td>16 (76)</td>
<td>9</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Lichtiger et al(^ {23})</td>
<td>4</td>
<td>13</td>
<td>11 (73)</td>
<td>5</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Keizer et al(^ {24})</td>
<td>2</td>
<td>31</td>
<td>24 (77)</td>
<td>–</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Caste et al(^ {25})</td>
<td>4</td>
<td>14</td>
<td>14 (100)</td>
<td>8</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

Weighted mean response: 71.4% (95% confidence interval, 0.67-0.75) (variable definition, most frequently pre-emption of colectomy).

### Table II. Controlled studies using intravenous cyclosporine (CyA) in the treatment of severe attack of ulcerative colitis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Randomized</th>
<th>Blind</th>
<th>Initial dose (mg/kg/day)</th>
<th>Patients (n)</th>
<th>Responders (%)</th>
<th>Response time (days)</th>
<th>Left-side colitis (patients, n)</th>
<th>Extensive colitis (patients, n)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Haens et al(^ {26})</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>14</td>
<td>9 (64)</td>
<td>5.2</td>
<td>2</td>
<td>12</td>
<td>Mono-therapy CyA, without steroids</td>
</tr>
<tr>
<td>Lichtiger et al(^ {27})</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>11</td>
<td>9 (81)</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>Methodologically important (see text)</td>
</tr>
<tr>
<td>Van Assche et al(^ {28})</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>35</td>
<td>30 (85)</td>
<td>–</td>
<td>18</td>
<td>17</td>
<td>Dose comparison study, 4 mg arm. Some patients received steroids, in well controlled study.</td>
</tr>
<tr>
<td>Van Assche et al(^ {29})</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
<td>38</td>
<td>32 (88)</td>
<td>4</td>
<td>22</td>
<td>16</td>
<td>4 mg arm. Some patients received steroids, in well controlled study.</td>
</tr>
<tr>
<td>Svanoni et al(^ {29})</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
<td>30</td>
<td>27 (90)</td>
<td>–</td>
<td>0</td>
<td>30</td>
<td>Comparison of CyA mono-therapy with CyA + corticoids. Not all patients refractory to steroids</td>
</tr>
</tbody>
</table>
these studies together, there were 128 patients included who were treated with intravenous CyA, 35 of them at a
dose of 2 mg/kg and the rest (93 patients) at 4 mg/kg. The
rate of response to the CyA alone, or in combination with
corticoids was 91.4% (95% CI, 0.85-0.95). Overall, in the
group receiving 2 mg/kg the rate of response was 85.7% (30/35)
and in the group of 4 mg/kg it was 93% (87/93).
However, in the study comparing the 2 doses head to
head, the tendency was the contrary, albeit not statisti-
cally significant.
Only one of this studies evaluated in a blind, randomized
and placebo-controlled trial, the efficacy of CyA in pa-
tients with severe flares refractory to steroids. This was
the study by Lichtiger et al, which we will analyze in
greater detail because of its importance. In this trial there
were 20 patients with severe attack (not only pancolitis
but also left-side colitis) who had not responded to treat-
ment with intravenous corticoids (dose equivalent to hy-
drocortisone 300 mg/day) over, at least, 7 days. Excluded
were the patients who had received treatment with purine
analogues in the previous 2 weeks and those with toxic
megacolon. The patients were randomized to receive
CyA (n = 11) at a dose of 4 mg/kg/day (intravenous con-
tinuous infusion) until a response was obtained up to a
maximum of 14 days, or placebo (n = 9). All the patients
received, as well, hydrocortisone (300 mg intravenous
daily). Mesalazine treatment was continued if previously
used, but not allowed the novo. The response to the treat-
ment was evaluated according to an index that had not
been validated and was based on a modification of True-
love-Witts index. At the conclusion of day 14, out of the
11 patients in the CyA group 9 responded (82%), compa-
ned to none in the placebo group, a difference which for-
ced the interruption of the trial after an interim analysis
or ethical grounds. There were no specific details on the
blood concentrations of CyA between the patients who respon-
ded and those who did not. Five of the patients who did
not respond in the placebo group and who did not require
emergency surgery were treated with CyA (cross-over)
and a response was obtained in all of them. Of the 9 pa-
tients who initially responded to CyA, one underwent an
elective colectomy and the rest were treated with oral
CyA at the initial dose of 6-8 mg/kg/day over 6 months.
Five maintain remission without steroids at 6 months and 3
relapsed in the course of the oral CyA treatment requi-
ring colectomy. As such, only the 45% of the patients
(3/11) who were initially treated with CyA avoided colec-
tomy in the 6 months of follow-up. In spite of the small
numbers, this remains a unique trial on methodological
grounds.
The second study compared steroid treatment versus CyA
in mono-therapy\cite{29}. Thirty patients were randomized
to CyA (4 mg intravenous) or 6 methylprednisolone (40 mg)
with responses being observed, after 8 days of treatment,
in 64.2% (9/14) and in 53% (8/15) in the 2 treatment
groups, respectively (p = 0.4). The patients included in
this study were not refractory to steroids. No serious drug-
related toxicity as observed with either treatment. After
one year, the 66% (10/15) and 60% (9/15) of patients of
CyA and steroids groups respectively avoid colectomy.
The third full study published compared the doses of
4 mg/kg versus 2 mg/kg of CyA\cite{30}. Seventy-three patients
were randomized to each treatment arm (38 to 4 mg/kg
and 35 to 2 mg/kg). The response was 84.2% (32/38) and
85.7% (30/35), respectively; the differences not being sta-
tistically significant. The adverse events were not clearly
higher in the higher-dose treatment group.
The controlled study published as a summary\cite{31} compared
the treatment of CyA (4 mg/kg) in mono-therapy against
CyA plus steroids. Thirteen of 15 patients in the first tre-
atment group responded compared to 14 of 15 in the
combination therapy group, all of whom with complete
response.

**Oral treatment**

In 9 studies\cite{27,28,29-31}, all of them non-controlled, the efficacy
of oral CyA was evaluated in patients with UC. In total,
there were 94 patients, some with moderate flare-ups, al-
though usually refractory to steroids. In several studies
there were no specific details on the extent of the disease
(at least in 23 patients the colitis was left-sided). The
doses employed varied between 4 and 10 mg/kg, with
5 mg/kg being employed in 6 of the 9 studies. The rate of
response was 71.2% (95% CI, 0.61-0.79), with response
being obtained in 67 of the 94 patients included. The
mean time-to-response, an aspect not specified in some
studies, was a weighted mean of 5.19 days (range 3.8 to
7 days). Table III reflects the more relevant aspects of the
articles evaluating oral CyA.

**Table III. Studies using oral cyclosporine for the treatment of severe ulcerative colitis attack**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Initial dose (mg/kg/day)</th>
<th>Patients (n)</th>
<th>Responders (%)</th>
<th>Response time (days)</th>
<th>Left-side colitis (patients, n)</th>
<th>Extensive colitis (patients, n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sood et al\cite{27}</td>
<td>4</td>
<td>6</td>
<td>5 (83)</td>
<td>3.8</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Davenport et al\cite{28}</td>
<td>5</td>
<td>14</td>
<td>7 (50)</td>
<td>7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fidanzo et al\cite{29}</td>
<td>5</td>
<td>10</td>
<td>2 (20)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Navarro et al\cite{30}</td>
<td>7</td>
<td>10</td>
<td>9 (90)</td>
<td>3</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Ott et al\cite{31}</td>
<td>5</td>
<td>5</td>
<td>4 (80)</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Actis et al\cite{27}</td>
<td>5</td>
<td>9</td>
<td>8 (88)</td>
<td>–</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Van Bodegraven et al\cite{28}</td>
<td>10</td>
<td>12</td>
<td>9 (75)</td>
<td>–</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Taylor et al\cite{29}</td>
<td>5</td>
<td>13</td>
<td>9 (69)</td>
<td>–</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Actis et al\cite{30}</td>
<td>5</td>
<td>15</td>
<td>14 (93)</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

*Weighted mean response: 71.2% (95% confidence interval: 0.61-0.79)*
This is a very important aspect but was not always fully detailed in some studies, making difficult to extract rele-
vant information. In some, there were no detailed descrip-
tions of the adverse effects while, in others, the acute
phase effects were mixed-in with those produced during
the chronic phase and patients with UC were mixed with
those with Crohn’s disease. Further, the percentage of
“patients with adverse effects” were not always calcula-
ted since sometimes only numbers (or percentages) were
provided for each adverse effect without specifying wheth-
er some patients had more than one of these adverse ef-
fects. Table IV summarizes the side effects reported, and
their frequencies.

In the studies with intravenous CyA, minor side effects
were more frequent. These included headache, hirsutism,
ion balance and hepatic enzyme alterations, elevation of
blood pressure and parasthesias, all of which were,
usually, easily controlled. The severe side effects are less
frequent and, among them, those that need to be highligh-
ted are nephrotoxicity, infections and neurotoxicity. Re-
garding to nephrotoxicity, although the transitory eleva-
tion of creatinine in plasma was common, in our review
there was only mentioned one case of severe acute renal
insufficiency, that finally was reversible[1]. Infections
were more frequent, and not only opportunistic germs and
sometimes severe, even leading to death. The first inclu-
ded 3 pneumonias caused by *Pneumocystis carinii*[11,20,22],
2 of them during the acute phase and one in the remission
phase, and one meningitis caused by *Listeria monocytoge-
gens*[12]. Among the infections caused by common patho-
gens in the studies included in our analysis were: one sep-
sis by *Staphylococcus aureus*[20], one infection by *Yersinia
ermosa*[12] and one by *Staphylococcus epidermidis* and
*Haemophilus influenzae*[21], this one after surgery and
which was fatal, and one case of pneumonia without mi-
crobiologic diagnosis[12]. Finally, severe neurotoxicity was
reported in some trials: 2 patients had seizures[1,2]. Of the
5 deaths during treatment with this drug in the patient se-
ries included in the analysis, 4 of them were during the acute
phase and the fifth[12] during the remission phase. The
causes of death during the acute phase were: one pneu-
monia caused by *P. carinii*,20 one sepsis caused by *S.
epidermidis* and *Haemophilus influenzae*[21], this one in a patient
who did not respond to CyA (had received only 48 h of
treatment)[20], one subarachnoid haemorrhage[1] and the last
by a deep vein thrombosis[15].

Although not specifically stated in detail in some studies
using oral CyA, adverse events seems clearly less fre-
et and minor: hirsutism, ion imbalance and slight in-
creases in plasma creatinine and blood pressure (table V).

We reviewed, as well, the clinical reports published of se-
vere secondary effects observed while using CyA in pa-
tients with UC[28,41]. All of these cases were infections, in-
cluding one case of pulmonary abscess from *Nocardia*
that responded well to treatment[41], one case of pneumonia
from *Aspergillus*[21], 3 cases of pneumonia from *P. carinii*
[11], but only one of them during the acute phase. All these
patients had been treated with parenteral CyA combined
with steroids. Apart from these cases, there were other si-
tilar ones, mainly infections (*Aspergillus*, disseminated and
fatal; mycotic aneurism), that had been reported in pa-
tients with Crohn’s disease treated with this drug.

DISCUSSION

Medical control of severe attack of UC using steroids is
not feasible in a considerable number of cases, and 30% to
50% of patients finally need colectomy[7]. CyA has been
used in this setting, but a systematic review of evidence
was not available. Although controlled data are limited, and
in fact we have found only one randomized study compar-
ing CyA to placebo[28], we can conclude from our
systematic review that there is compelling evidence for
using CyA in the treatment of steroid-refractory acute se-
vere attacks of UC. Data from roughly 600 patients repor-
ted in literature are very consistent, and both observational
and controlled data suggest a 60-70% effectiveness, defi-
ned as avoidance of colectomy, of the drug in this particu-
lar clinical setting. Furthermore, available data from a
controlled trial indicate that a 2 mg/kg dose is as effective
as 4 mg/kg, previously considered as standard[16]. Some ot-
er data from uncontrolled studies also show high effecti-
veness with low toxicity with the lower (2 mg/kg/day) intravenous dose[11,41]. In our view these
data support the recommendation of an initial course of

### Table IV. Adverse events of cyclosporine (CyA) recorded in the studies analyzed

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Number of patients (CyA (oral route)</th>
<th>CyA (oral route)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Meningitis from <em>L. monocytogenes</em></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Convulsions</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pneumonia from <em>PC</em></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Infection by DC</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Spinal abscess</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
| Hepatic enzyme alter-
ations                  | 11                               |                 |
| Blood pressure        | 37                               | 3               |
| Parasthesias          | 29                               |                 |
| Rash                  | 1                                |                 |
| DVT                   | 2                                |                 |
| Raised creatinine     | 23                               | 3               |
| Vomiting              | 4                                |                 |
| Hyperglycemia         | 5                                |                 |
| Gingival hyperplasia  | 2                                |                 |
| Ion imbalance         | 6                                | 7               |
| Myelo-suppression     | 2                                |                 |
| Fever                 | 4                                |                 |
| Allergy               | 1                                |                 |
| Bronchospasm          | 2                                |                 |
| Heparox asier         | 1                                |                 |

**ARI:** acute renal insufficiency; **PC:** *Pneumocystis carinii*; **DC:** difficult

**Controlled;** **DVT:** deep vein thrombosis; **i.v.:** intravenous.

**Table IV.** Adverse events of cyclosporine (CyA) recorded in the studies analyzed.
2 mg/kg that could be adjusted according to blood levels\(^{13}\). So, in most acute severe bouts of UC CyA should be added to steroids if clinical remission is not obtained in 3 to 7 days, and surgery is not mandatory because of complications (massive bleeding or bowel perforation).

Some data suggest that CyA is under-used and, sometimes, administered too late in the treatment of severe attack of UC\(^{16}\). Probably, there are several factors that can explain this restrictive policy in clinical practice: a) the possibility of important adverse events, above all, of severe infections; b) the lack of efficacy over the long-term; and probably not the least important c) the lack of experience of the gastroenterologist in the use of CyA.

Regarding to the safety of the drug, our study shows (as do others), that the most frequent adverse effects are mild infections; surgery, later. The concept that surgery cures the colon is conserved and the activity of the disease is reduced. Flare-up, the rate of relapse decreases and avoid surgery when practically all the patients are receiving concomitant treatment with high-dose steroids, drugs which are associated with a significant risk of infection. A final point needs to be made and that is whether an earlier introduction of CyA into the treatment scheme would offer a better control of the disease, decreasing the requirements for steroids and, as such, the risk of infection. Using 2 mg/kg/day dose may theoretically decrease adverse event without decreasing effectiveness, although some secondary effects and deaths are in the non-acute phase including some without CyA treatment. i.v.: intravenous.

### Table V. Adverse events recorded in the treatment of ulcerative colitis with cyclosporine (CyA)

<table>
<thead>
<tr>
<th>Authors</th>
<th>CyA initial dose</th>
<th>Adverse event</th>
<th>Age (years)</th>
<th>Other drugs</th>
<th>Deaths</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stack et al(^{28})</td>
<td>i.v. 4</td>
<td>Pulmonary abscess (Nocardia)</td>
<td>68</td>
<td>Corticoids</td>
<td>No</td>
<td>Responded to i.v. CyA but pulmonary abscess developed on day 18.</td>
</tr>
<tr>
<td>Caroli et al(^{27})</td>
<td>i.v. 4</td>
<td>Pneumonia (Aspergillus)</td>
<td>51</td>
<td>Corticoids</td>
<td>No</td>
<td>Responded to i.v. CyA but pneumonia developed 3 weeks after discharge from hospital</td>
</tr>
<tr>
<td>Hintereiter et al(^{29})</td>
<td>i.v. 4</td>
<td>Septicemia (Staphylococcus aureus)</td>
<td>64</td>
<td>YES</td>
<td></td>
<td>Not directly related: 14 months later without further treatment</td>
</tr>
<tr>
<td>Quan et al(^{30})</td>
<td>i.v. 4</td>
<td>Pneumonia (Pneumocystis carinii)</td>
<td>63</td>
<td>Corticoids</td>
<td>Yes</td>
<td>Responded initially to i.v. CyA but re-hospitalized due to pneumonia 6 days after discharge; death resulted</td>
</tr>
<tr>
<td>Smith and Hanauer(^{10})</td>
<td>i.v. 4</td>
<td>Pneumonia (Pneumocystis carinii)</td>
<td>32</td>
<td>Corticoids</td>
<td>Yes</td>
<td>Responded to i.v. CyA but, once out of acute phase contracted pneumonia, and died</td>
</tr>
<tr>
<td>Scout et al(^{31})</td>
<td>i.v. 4</td>
<td>Pneumonia (Pneumocystis carinii)</td>
<td>43</td>
<td>Corticoids</td>
<td>No</td>
<td>Responded to i.v. CyA and surgery was scheduled. Contracted pneumonia post-surgery, still without further treatment</td>
</tr>
</tbody>
</table>

Some secondary effects and deaths are in the non-acute phase including some without CyA treatment. i.v.: intravenous.
tocols and guidelines; and c) collaborating with specialists who are experts in the use of CyA (nephrologists, immuno-
ologists or hepatology colleagues experienced in liver transplantation). Different solutions would be appropriate,
depending on the local circumstances. It would be easy to consult with a colleague in another centre regarding any
doubts, and this would encourage safe use of the drug. In conclusion, it is evident that CyA is not the definitive treat-
ment for severe attack of UC, but it can be very use-
ful in some cases and we need to consider seriously its use in all such patients. The local hospital circumstances,
and that of each patient, can tip the balance towards this
pharmaceutical agent or towards surgery (or other alter-
 natives which, at the moment, are experimental), bearing in
mind the arguments for and against its use. In many
patients with severe attack of UC, CyA is the most rea-
noney therapeutic alternative, above all taking into ac-
count that its pre-operative use does not increase the risk
of mortality of subsequent surgery, if needed. Elective
surgery can then, proceed with the patient in a better cli-
 nical condition.
In summary, from the data available in the literature, we
suggest the following points to optimize the use of CyA:

1. Guided use. The protocol needs to be followed syste-
matically to avoid toxic effects, or at least to minimize them. Monitoring drug levels, and active surveillance of
abnormal events, either those severe as renal toxicity, neu-
rotoxicity and infections as those minor but more fre-
quently, is essential. We recommend, in spite of other au-
thors, to use the intravenous route to avoid problems with
intestinal absorption.

2. Early administration. The decision to use CyA should
not be delayed too long, after 3-5 days without response to
intravenous steroids should be decided to use or not CyA. The Oxford protocol showed that with a systematic
approach, the treatment clearly improves the mortality
rate. Very probably, to prolong a non-effective steroid
treatment is the determinant of poor prognosis in some of
these patients.

3. Use of azathioprine. If remission has been achieved with CyA, the patient should receive maintenance treat-
ment with azathioprine (or 6-mercaptopurine) to reduce the risk of relapse, usually followed by colectomy.

4. An initial dose of 2 mg/kg/day dose appears reasonable
in an intent to minimize the side-effects.

REFERENCES

1. Edwards FC, Truelove SC. The course and prognosis of ulcera-
2. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final re-
3. Truelove SC, Jewell DP. Intensive intravenous regimen for se-
4. Kornbluth A, Marion JR, Salomon P, Janowitz HD. How effec-
tive is current medical therapy for severe ulcerative colitis and
5. Pession DC, May GT, Glick G, Sutherland LR. Azathioprine para
el mantenimiento de la remisión en la enfermedad de Crohn (Translated Cochrane Review). In: The Cochrane Library. Ox-
ford: Update Software. CD000567-ES. CD000567-ES.