THE TREATMENT OF LYELL’S SYNDROME: OUR EXPERIENCE

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SUMMARY. In view of the pathogenic mechanisms of Lyell’s syndrome, we consider support-only treatment to be insufficient and believe it is necessary to administer i.v. human immunoglobulin. Because of the potentially severe side effects of the high doses usually recommended, we prefer to use low doses (no more than 5 g per day) in association with the administration of fresh frozen plasma, which offers the benefits of the high protein content in the albumin (with its resuscitative function) and its globulin content (functioning as a specific therapy for Lyell’s syndrome). We present the latest cases we have observed and treated using this protocol.

Lyell’s syndrome is an adverse reaction to drugs which, apart from affecting blood and coagulation, mainly targets the cutaneous, respiratory, digestive, and urinary epithelium.

In forms presenting non-immune pathogenesis (patients with AIDS), where enzymatic defects prevent both the normal metabolism of drugs administered in large quantities and the detoxification of reactive products, as also the anti-infective administration of IgIV, plasmapheresis would appear to be the treatment of choice.

In the immune variants, two pathogenic patterns are described:
1. perforin-granzyme mediated cell apoptosis;
2. Fas-Fas-L mediated cell apoptosis.

Of these two, in Lyell’s syndrome, apoptosis due to disequilibrium of the Fas-Fas-L system would appear to prevail (in which the former is the receptor of cell death and the latter is its ligand), owing to Fas-L over-regulation caused by secretion of cytokines (TNF-alpha).

It is this pathogenic mechanism that makes treatment with i.v. human immunoglobulin specific for Lyell’s syndrome: the antibodies contained in the immunoglobulin preparations, because of their competition at the level of receptors with Fas-L, block the cell apoptosis process.

The suggested dose, for three or four consecutive days, is however very high (0.2-0.75 g/kg per day); in addition, following the administration of high doses, considerable side effects have been described, also in pathologies other than Lyell syndrome.

These include:
1. aseptic meningitis, with severe cephalgia, especially in patients with a positive anamnesis for hemi-cranial attacks;
2. severe anaphylactic reactions, especially in patients with IgA deficit and the presence of anti-IgA antibodies, which form immune complexes with activation of the complement with IgA contained in the immunoglobulin preparations;
3. haematic hyperviscosity syndrome, with cerebral ictus, myocardial infarction, and jugular thrombosis, especially in elderly patients or patients with extensive vascular disease due to increased risk of thromboembolus;
4. acute renal failure caused by osmotic problems in the proximal tubule owing to the use of IgIV containing sucrose.

Table I presents the data of patients treated with high doses of IgIV.

Table I - Some case histories regarding use of IgIV

<table>
<thead>
<tr>
<th>Authors and bibliographical reference</th>
<th>Year</th>
<th>Number of cases</th>
<th>Days of therapy</th>
<th>Doses</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viard et al.\textsuperscript{a}</td>
<td>1998</td>
<td>10</td>
<td>4</td>
<td>0.2-0.75 g/kg per day</td>
<td>-</td>
</tr>
<tr>
<td>Morici et al.\textsuperscript{b}</td>
<td>2000</td>
<td>7</td>
<td>3</td>
<td>1.5-2</td>
<td>-</td>
</tr>
<tr>
<td>Paquet et al.\textsuperscript{c}</td>
<td>2001</td>
<td>1</td>
<td>5</td>
<td>0.75</td>
<td>-</td>
</tr>
<tr>
<td>Tristani-Firouzi\textsuperscript{d}</td>
<td>2002</td>
<td>8</td>
<td>4</td>
<td>0.5-0.75</td>
<td>-</td>
</tr>
<tr>
<td>Trent et al.\textsuperscript{e}</td>
<td>2003</td>
<td>16</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prins et al.\textsuperscript{f}</td>
<td>2003</td>
<td>48</td>
<td>4</td>
<td>0.75</td>
<td>6</td>
</tr>
<tr>
<td>Bacchot et al.\textsuperscript{g}</td>
<td>2003</td>
<td>34</td>
<td>2</td>
<td>1</td>
<td>11 (32%)</td>
</tr>
<tr>
<td>Al-Mutairi et al.\textsuperscript{h}</td>
<td>2003</td>
<td>12</td>
<td>4-5</td>
<td>0.5-1</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Predicted mortality (SCORTEN): 8.2 (24%)
As can be seen, in one of the most numerous collections of case histories, actual mortality (32%) exceeded predicted mortality (24%), which led the authors of the study to the conclusion that treatment with IgIv had no effect on the reduction of mortality or the progress of the disease, even if the majority of deaths occurred in elderly patients or patients suffering from kidney failure.

Currently, in the wake of initial enthusiasm, and in the absence of the proven effectiveness of IgIv, it remains to be demonstrated in more extensive trials that support therapy is the only valid therapy. It is probably more reasonable to envisage a non-routine use of IgIv, also in consideration of the severe side effects it can cause. But it is also possible to picture a treatment with low doses of IgIv, on the strength of experience with certain therapies of dermatological pathologies of various nature. It thus proved possible to successfully treat a case of acquired bullous epidermolysis, as also a case of pemphigus foliaceus. Recently, in a case of a very extensive pemphigus vulgaris, we successfully used low doses of IgIv (no more than 5 g per day) in association with fresh frozen plasma and as an adjuvant to reduce the dose of steroids and immunosuppressants. The last patients suffering from Lyell syndrome that we treated received low doses of IgIv associated with fresh frozen plasma. This has a three-fold purpose:

1. to supply resuscitation fluids owing to the increase of volaemia due to the high protein content;
2. to supply a specific treatment for the high presence of immunoglobulins; and
3. to reduce the dose of IgIv or to replace its action when suspended.

Table II presents the cases we have observed over the course of the years, the kind of treatment carried out, and the number of deaths. Table III presents the specific characteristics of every patient treated with immunoglobulins and fresh frozen plasma.

As can be seen, the patient who did not survive presented numerous considerable risk factors (advanced age and serious pre-existing pathology). The delay before such patients are generally transferred after onset of the disease is also noteworthy. It is precisely this delay that often prevents proper recording of the parameters that need to be taken into consideration for the use of SCORTEN, with the dual aim of assessing the prognosis in individual cases and of comparing cases treated with different therapies.

Table II - Treatment over the years

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Period</th>
<th>Treatment</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Until 1991</td>
<td>Steroids</td>
<td>5 (71.4%)</td>
</tr>
<tr>
<td>13</td>
<td>Until 2000</td>
<td>Support therapy</td>
<td>5 (38.4%)</td>
</tr>
<tr>
<td>5</td>
<td>From 1997 local therapy with homologous keratinocytes</td>
<td>Low doses of IgIv + fresh frozen plasma</td>
<td>1 (20%)</td>
</tr>
</tbody>
</table>

Table III - Patients treated with IgIv (5 g per day) and fresh frozen plasma

<table>
<thead>
<tr>
<th>Year</th>
<th>Age (yr)/sex</th>
<th>Cause</th>
<th>Diseases</th>
<th>Complications</th>
<th>Delay in hospitalization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>56, M</td>
<td>Allopurinol</td>
<td>Atrial fibrillation</td>
<td>Hepatitis/pancreatitis</td>
<td>2 days</td>
<td>Alive</td>
</tr>
<tr>
<td>2002</td>
<td>73, F</td>
<td>Allopurinol</td>
<td>Atrial fibrillation</td>
<td>Kidney failure</td>
<td>3 days</td>
<td>Alive</td>
</tr>
<tr>
<td>2003</td>
<td>82, F</td>
<td>Diclofenac</td>
<td>Chronic respiratory and cardiac insuff.</td>
<td>Cardiac decompensation</td>
<td>2 days</td>
<td>Deceased</td>
</tr>
<tr>
<td>2003</td>
<td>67, F</td>
<td>Phenobarbital</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Septicaemia</td>
<td>8 days</td>
<td>Alive</td>
</tr>
<tr>
<td>2004</td>
<td>8, F</td>
<td>Bimatoprost</td>
<td>Plaque sclerosis</td>
<td>Septicaemia</td>
<td>5 days</td>
<td>Alive</td>
</tr>
</tbody>
</table>

RéSUMÉ. En considération des mécanismes pathogéniques du syndrome de Lyell, les Auteurs jugent que le traitement qui consiste seulement en le seul support est insuffisant et qu’il faut administrer l’immunoglobuline humaine par voie intraveineuse. A cause des effets collatéraux potentiellement sévères des dosages élevés normalement recommandés, il préfèrent utiliser des dosages limités (maximum 5 g par jour) en association avec l’administration de plasma frais congelé, ce qui offre les avantages du contenu élevé protéique de l’albumine (avec sa fonction réanimatrice) et de son contenu de globuline (qui agit comme thérapie spécifique dans le syndrome de Lyell). Les Auteurs présentent les cas les plus récents qu’ils ont observés et traités utilisant de protocole.
BIBLIOGRAPHY


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