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 resuscitatory 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,[1-4] mainly targets the cutaneomucous, respiratory,[5] digestive,[6] and urinary[7] epithelium.

In forms presenting non-immune pathogenesis (patients with AIDS), where enzymatic defects prevent both the normal metabolization of drugs administered in large quantities and the detoxification of reactive products,[8] 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.[9]

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:[10] 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 cephalea, especially in patients with a positive anamnesis for hemicranial 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.[11]

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

Table I - Some case histories regarding use of IgIv

Authors and bibliographical reference	Year	Number of cases	Days of therapy	Doses	Deaths
Viard et al.[10]	1998	10	4	0.2-0.75 g/kg per day	-
Morici et al.[12]	2000	7	3	1.5-2 "	-
Paquet et al.[13]	2001	1	5	0.75 "	-
Tristani-Firouzi[14]	2002	8	4	0.5-0.75 "	-
Trent et al.[15]	2003	16	4	1 "	1
Prins et al.[16]	2003	48	4	0.75 "	6
Bacchot et al.[17*]	2003	34	2	1 "	11 (32%)
Al-Mutairi et al.[18]	200	12	4-5	0.5-1 "	-

* Predicted morality (SCORTEN): 8.2 (24%)

Table II - Treatment over the years

Number of patients	Period	Treatment	Deaths
7	Until 1991	Steroids	5 (71.4%)
13	Until 2000	Support therapy	5 (38.4%)
	From 1997 local therapy with homologous keratinocytes		
5	Until the present day	Low doses of IgIv + fresh frozen plasma	1 (20%)

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

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

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.[17]

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,[19] as also a case of pemphigus foliaceus.[20] 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.[21]

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,[22] with the dual aim of assessing the prognosis in individual cases and of comparing cases treated with different therapies.

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 recommandes, ils préfèrent utiliser des dosage 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.

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