TREATMENT OF PROLIFERATIVE LUPUS NEPHRITIS WITH CYCLOPHOSPHAMIDE

Andreea Munteanu, A. Caraba, I. Romosan

DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF MEDICINE AND PHARMACY „VICTOR BABEŞ” TIMIŞOARA

Summary

Lupus nephritis (LN) is one of the most severe and common manifestations of SLE, being a major cause of morbidity and death. Renal impairment plays a determinant role in the development of the disease, renal failure being one of the main death causes in SLE. The incidence of LN varies according to the diagnostic methods used. When diagnosis is established solely based on clinico-biological criteria, the incidence of LN ranges between 60 and 80%. On the other hand, diagnosis established on the basis of the histological exam of the kidney fragment obtained by renal needle biopsy shows that LN has an incidence ranging between 95 – 100%. The aim of the study is to underline the role of the histological exam in establishing the diagnosis of LN and the effectiveness of low-dose treatment with cyclophosphamide associated with metylprednisone versus the standard therapy. The study was conducted on thirty patients (all females) suffering with SLE with kidney impairment, admitted in the Timisoara Railways Hospital between 2007 and 2011. Renal needle biopsy was performed for all patients in order to establish an accurate diagnosis of LN. Proteinuria, haematuria and creatinine clearance were determined at the beginning of the study and after treatment. The group of patients was divided into two sub-groups which were treated with different doses of cyclophosphamide associated with metylprednisone (standard doses vs. low doses). After performing renal needle biopsy, only 18 patients remained in the study group, i.e., those with proliferative LN. The mean age was 37 years. There was a significant correction of the values of proteinuria and creatinine clearance after treatment, both in sub-group 1 (the NIH Protocol) and in sub-group 2 (the Euro-Lupus Protocol). The results obtained by using both types of protocols were statistically insignificant (p<0.01). The histological exam ascertains the positive diagnosis of lupus nephritis, assesses the class and stage of the disease, and offers prognostic information, thus guiding therapy.

Key words: systemic lupus erythematosus, lupus nephritis, renal histopathological exam, induction therapy.

narita_andreea@yahoo.com

Introduction

Systemic lupus erythematosus (SLE) is a disorder without unknown cause, autoimmune pathogenesis, characterised by a chronic inflammatory process associated with the production of antibodies (Ab) directed against nuclear, cytoplasmic and membranous antigens (Ag). (Wallace et al., 2007).

The clinical picture has a great diversity, reflecting the chronic inflammation of various organs and systems. The most affected organs seem to be the skin, the joints and the kidneys. Kidney impairment (lupus nephritis – LN) is one of the most common and most severe manifestations of SLE, representing a major cause of morbidity and mortality. (Kotzin., 1996).

All renal structures may be affected in LN: the glomeruli (the most severe impairment), the tubes, the interstitium and the vessels. Although glomerular impairment has an extreme prognostic importance, some of the patients presented severe tubulo-interstitial or vascular...
impairment, despite only slight glomerular impairment (Caraba et al., 2009).

The clinico-biological picture of LN varies from isolated urinary disorders to rapidly progressive renal failure. For an accurate diagnosis of LN, prognosis and the ensuing therapy, as well as the histopathological exam are obligatory. (Cagnoli, 2003)

The incidence of NL may also vary, according to the diagnostic methods used. When diagnosis is based on clinico-biological criteria, the incidence of LN varies between 60 and 80%, while a diagnosis based on the histological exam of a kidney fragment obtained by renal needle biopsy (RNB) indicates an incidence of LN between 95 – 100%.(Zabaleta et al., 2003; Cameron, 1999).

Studies have shown that delayed treatment leads to a negative response in the long term, thus requiring a prompt diagnosis of the histological type and immediate setting up of proper treatment.

The practical approach in the pathogenetic treatment of LN requires a remission induction therapy and a maintenance therapy. The induction therapy is directed towards the proliferative histological types of LN (types III and IV). In clinical practice, the treatment of LN follows the recommendations of the National Institute of Health (NIH) and the Euro-Lupus-Trial.

The aim of the study is to underline the role of the histological exam in establishing the diagnosis of LN, and in assessing the effectiveness of the classical treatment with high doses of cyclophosphamide (NIH protocol) versus low-dose treatment (the Euro-Lupus protocol).

Material and methods

The study was conducted on thirty patients (all females) suffering with SLE with kidney impairment. All the patients were admitted in the Timisoara Railways Hospital between January 2007 and December 2011.

All the patients met the ARA diagnostic criteria for SLE. The exclusion criteria consisted of: pregnancy, SLE-associated bleeding diathesis, uncontrolled high blood pressure (BP), the patient’s refusal.

The clinico-biological assessment of the patients was carried out when the patients were included in the study and at the end of the induction therapy.

a) Index of renal involvement:
- proteinuria (the Turbidimetry method, normal values NV<200mg/24h)
- haematuria (the Addis-Hamburger method, NV H<1000 red blood cells/minute)
- creatinine clearance (ml/min/1.73 mp) = urine creatinine (mg/dl) x urine volume (ml)/serum creatinine (mg/dl) x collection time (minute = 1440 minutes/24hs).

b) Renal biopsies:
- kidney biopsy was performed using a Tru Cut biopsy needle. The biopsy fragments were stained with hematoxylin-eosin and PAS and analysed under an optic microscope. The fragments were classified according to the ISN/RPS classification for LN (2003).

Based on the resulting histological types, the study retained only the patients with proliferative LN: histological types III and IV (focal LN and diffuse LN). Induction treatment addresses this class of patients.

c) Protocol therapeutic:
- this group of patients was divided into two subgroups (subgroup 1 and subgroup 2), each subgroup following a different induction therapeutic protocol:
  1. The standard protocol (NIH):
     - Cyclophosphamide, in monthly iv doses of 0.5-1 g/m² body surface, for 6 months, associated with
     - Methylprednisolone, iv 1 g/day for 3 consecutive days, followed by Prednisone 0.5-1 mg/kg/day, the initial dosage being gradually decreased.
  2. The Euro-Lupus-Trial Protocol (low doses of Cyclophosphamide):
Cyclophosphamide, 6 doses of 0.5 g, every other week, associated with Methylprednisolone, iv, 1 g/day for 3 consecutive days, followed by Prednisone 0.5-1 mg/kg/day, the initial dosage being gradually decreased.

d) Statistical analysis:
- all the numerical values were expressed as mean value ± standard deviation (SD). The statistical analysis was based on Student’s T Test, with p<0.05 considered statistically significant.

Results and discussion
Eighteen patients remained in the group after RNB and after having determined the histological type:
- 4 patients (13% of the total number of patients) belonging to the histological type III (focal LN)
- 14 patients (46% of the total number of patients) belonging to the histological type IV (diffuse LN)

Renal needle biopsy revealed that 60% of the patients had some form of proliferative LN.

After having randomly divided the patients in two subgroups, we obtained the following clinico-biological parameters for the assessment of the renal function (Table 1).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.77±6.28</td>
<td>40.22±6.03</td>
</tr>
<tr>
<td>Histological type III (No. patients)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Histological type IV (No. patients)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.68±1.61</td>
<td>1.96±1.86</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>84±33.15</td>
<td>77.33±31.60</td>
</tr>
<tr>
<td>Proteinuria (mg/24h)</td>
<td>2811±1215</td>
<td>2594±1200</td>
</tr>
<tr>
<td>Haematuria (red blood cells/minute)</td>
<td>2438±1136.27</td>
<td>2800±1373.86</td>
</tr>
</tbody>
</table>

The initial values of the proteinuria, haematuria and creatinine clearance (before beginning therapy) were similar in both sub-groups (Fig. 1).

Fig.1

After beginning the treatment, there was a significant correction of the values of proteinuria and creatinine clearance both in subgroup 1 (NIH Protocol), and in subgroup 2 (the Euro-Lupus Protocol). The differences between the two types of protocols were statistically insignificant (p>0.05). (Fig.2, Fig.3)

Fig.2

The mean value (±DS) of proteinuria for both sub-groups, at the beginning and after treatment. (p=0.479)

Fig.3

The mean value (±DS) of creatinine clearance for both sub-groups, at the beginning and after treatment. (p=0.494)
The evolution of the patients under induction treatment was good, showing a significant improvement of the values of proteinuria, haematuria and creatinine clearance after treatment with cyclophosphamide associated with prednisone.

The histological exam of the impaired organs shows the presence of immune complexes and complement fractions at this level. The kidney represents the main target of CIC.

Lupus nephritis (LN) is one of the most severe and common manifestations of SLE, being a major cause of morbidity and death (Romosan et al., 2002).

Renal impairment plays a determinant role in the development of the disease, renal failure being one of the main death causes in SLE (Moroni et al., 2004).

Several studies have shown that a diagnosis established solely on the basis of clinicobiological data can be inconclusive (Mittal et al., 2005; McLaughlin et al., 1994; Caraba et al., 2006)

Renal biopsy is worthwhile in all patients with lupus who have abnormal urine and/or reduced renal function because it provides prognostic information and influences initial treatment. The overriding characteristic of lupus nephritis is its variability, between patients, within biopsies, and even within glomeruli (Cameron, 1999).

From a clinico-biological point of view, LN may manifest itself in several ways. Proteinuria is present in almost every patient, with varying intensity that may reach the nephrotic level. Electrophoresis shows the presence of unselective or mixed glomerular proteinuria, rarely tubular proteinuria, depending on the histological structures that were mostly affected. Another urinary sign is microscopic haematuria (in very rare cases, it may be macroscopic). High blood pressure is associated with severe LN and oedemas indicate the presence of nephrotic syndrome. Nicturia is characteristic for the tubulo-interstitial impairment. Azotemia is an indicator of renal failure. In some cases, LN may set on taking the form of acute renal failure commonly associated with other severe manifestations (myocarditis, disorder of the central nervous system) (Edworthy, 2007).

The treatment of LN still remains a challenge, although the aggressive use of immunosuppressors improved both the survival rate and the progression of kidney destruction, as the good results minimised certain therapy-induced adverse effects. This is why recent studies have tried to define alternative therapeutic protocols which could effectively induce remission and maintain it and, at the same time, have a lesser toxicity than the standard therapy (Dolff et al., 2010)

The present study showed a similar effectiveness in remission induction both with the standard therapeutic protocol (NIH) and with the Euro-Lupus protocol which uses low doses of cyclophosphamide (thus, less toxic), the differences being statistically insignificant both for proteinuria and for creatinine clearance ($p<0.05$).

Systemic lupus erythematosus (SLE) represents the prototype of the autoimmune disease associated with the production of antibodies directed against nuclear, cytoplasmic and membranous antigens (Wallace et al., 2001).

**Conclusions**

The histopathological exam is necessary in the evaluation of any LN patient because it confirms with certainty the positive diagnosis of lupus renal disease, assesses the class stage of the disease, thus offering prognostic information and determining therapy.

The association of cyclophosphamide with methylprednisolone has similar results in the treatment of proliferative LN both in patients treated with standard doses and in those treated with low doses (low toxicity).
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