Treatment of Patients with Lupus Nephritis

J.N. Boletis
Department of Nephrology and Transplant Center, Laiko Hospital, Athens

In systematic Lupus Erythematosus (SLE) there is clinical renal involvement in 40% of cases [1,2]. With today`s therapeutic protocols the five year survival rate exceeds 90% and the fifteen year survival approaches 80% [3]. When however the disease is complicated by severe glomerulonephritis (GN) the five year survival with preservation of renal function is reduced to 60% [4].

Among patients with SLE, those who demonstrate progression to end stage renal failure usually develop a variety of proliferative GN type III or IV according to the classification of the World Health Organization (WHO) [5]. The recognition of the prognostic significance of proliferative lesions led to the changed WHO classification of the nephritides of lupus in 1995 [6]. According to this, membranous GN with proliferative changes, is grouped, according to the extent of the lesions, into group III or IV, focal or diffuse proliferative GN respectively, and is treated accordingly. In cases however of GN type III with mild focal lesions which are local and involve less than 25% of the glomeruli, the prognosis is considerably better and the treatment less aggressive [7].

The therapy of the proliverative types of lupus nephritis with relatively high doses of corticosteroids (CS) between 40 and 60mg daily, which was introduced at the beginning of the sixties, improved the prognosis in comparison with the use of smaller doses [8]. From that time and up until today CS are considered a basic part of the treatment of the SLE GN.

The use of immunosuppressive drugs in the treatment of severe lupus nephritis started in the nineteen sixties. Early studies of the use of Azathioprine (AZA) [9-11] or Cyclophosphamide (CY) [12-16] in combination with CS led to the conclusion that the combination of these drugs was more effective than CS alone, both for improvement in renal function and for patient survival. Other reports did not show the same benefits.All the studies from that period however have been criticised for defective study structure, small numbers of patients and short follow-up times as well as for the lack of information on the heterogeneity of the renal morphology. In 1975 a small prospective study was published from the National Institute of Health (NIH) in the USA [12]. In this study, 38 patients received either 0.5mg/Kg prednisone alone or in combination with CY or AZA in a randomized manner. Despite the fact that the patients on prednisone alone had a more rapid worsening of their renal function than those who took immunosuppressive therapy, the authors came to the conclusion that the latter added only marginally to the control of the disease.

After the disagreements between the results of the various studies [17], a meta–analysis showed that patients who received a combination of immunosuppressive drugs and CS had a significantly lower probability of developing renal failure in comparison to those who received only CS [18]. This clinical finding was also verified in a study where repeated renal biopsies were performed [19]. In 1986, the authors of the latter study, who were from the NIH, published the first results of a large randomized study in which patients with severe lupus nephritis were treated with one of five different therapy protocols: prednisone alone or in combination with AZA, oral CY, AZA and oral CY , and intravenous (i.v.) CY [20]. The results of this study showed that the probability of the development of end stage renal failure within five years was the same for all groups. After 10 years however, CS with i.v. CY led to a better renal survival than prednisone alone [21]. Despite the fact that the other combinations were not significantly different in their constitution from the CS+i.v.CY they proved less effective, especially the CS+AZA combination, than CS+i.v.CY. More recently. The NIH group published the results of a comparative randomized trial in which the effectiveness of i.v. methylprednisolone (MP) (1g MP/m^2 per month on three consecutive days, followed by 1g/m^2 for six months in 25 patients) was compared to two different CY protocols [22]. The “short term” CY protocol consisted of monthly i.v. injections of 0.5-1.0g/m^2 CY for 6 months (20 patients) and the “long term” CY consisted of monthly infusions of 0.5-1.0g/m^2 for 6 months followed by infusions of the same dose every three months for 2years (20 patients). Patients admitted to this trial had severe lupus nephritis and had mean serum creatinine levels of 165μmol/L. They were followed up for a mean period of three years. Patients treated with i.v. MP alone had a significantly higher probability of doubling their serum creatinine levels in comparison with the group who received long term CY . There was no statistically significant difference between the two CY therapy groups as far as serum creatinine levels was concerned but the probability of extrarenal relapse resistant to high doses of CS was significantly lower in the long term CY therapy group.

In another recent meta-analysis which included 19 prospective trials in 440 patients, the combination of immunosuppressive drugs and prednisone reduced the incidence of end stage renal disease and the total morbidity when compared with isolated prednisone therapy [23]. No significant differences were observable between the various immunosuppressive therapy protocols which included AZA or oral CY or the combination of AZA and CY or i.v. CY. It is worthy of note that i.v. CY did not offer any advantage over the other imunosuppressive protocols as measured by the incidence of end stage renal failure or total morbidity. The influence however of the NIH studies was enormous. Today the combination of prednisone and i.v. CY long term proto-

col constitutes the therapy of choice for proliferative lupus GN. The long follow-up period and the relatively large number of patients included in the studies made the NIH studies unique. In the adoption of the long term i.v. CY protocol the reported reduced toxicity of iv. CY in comparison with the oral route was significant [24].

Despite the widespread acceptance and application of the combination of CS+iv.CY, many questions, such as the duration of therapy required to reduce the incidence of relapses or the length of treatment required to produce a second remission after relapse, remain unanswered. For this reason we recently studied the indicators of remission, of relapse and second remission in a population of 85 patients with histologically verified proliferative lupus GN who had been treated with the combination of CS and iv.CY [25]. It was found that the mean time to remission in these patients was 10 months, while 22% of the patients were still not in remission after 2 years. Negative prognostic indicators for the achievement of remission were delay in the initation of therapy after the diagnosis of nephritis and the higher degree of proteinuria. Of the 63 patients who achieved remission, 23 relapsed at a mean time of 79 months. For these patients indicators of early relapse were a greater length of time to first remission a history of central nervous system involvement and the histological type of the renal lesions. Patients with WHO classification type IV lesions relapsed later. The mean duration of a second remission was 32 months and, with three exceptions, all patients took a longer time to achieve the second remission than the first. The length of time to achieve a second remission was longer in those patients with a longer time to first remission, who had an early relapse and in those with chronic changes on renal biopsy material. Thus it would seem that to achieve remission in many patients with lupus nephritis who are being treated for the first time and in most of those being treated for the second time, relatively long term therapy will be needed which will be accompanied unavoidably by cumulative toxicity.

It is obvious therefore that alternative treatment with the same or better therapeutic responses and less toxicity than CY should be sought. With this in view we compared the iv. administration of the immunoglobulin Sandoglobulin (IVIG) with iv. CY for the maintainance of remission of proliferative lupus GN[26]. This was a preliminary study in 14 patients with lupus nephritis type III or IV who had been treated by CS and 6 monthly boosters of iv.CY. Following this, and with the prerequisite that the disease was in remission the patients were randomized to monthly IVIG for 18 months or to iv.CY every 2 months for 6 months and then every 3 months for 12 months. The accompanying dose of CS was varied according to the clinical progress of the disease according to the opinion of the treating physician. At the end of the study there was no significant difference between the two groups in regard to serum creatinine levels or creatinine clearances nor in the degree of proteinuria measured.

In a recent publication from Hong Kong, the results of the use of mycophenolate mofetil (MMF) in the treatment of diffuse proliferative lupus nephritis have been reported in a protocol which consisted of CS and MMF for 12 months, in comparison with a second protocol of CS with oral CY for 6 months folowed by CS with AZA for 6 months (27). In the 21 patients in the MMF group 81% achieved complete remission and 14% a partial remission in comparison with 76% and 14% respectively in the CS+CY/CS+AZA. There was no difference in serum creatinine levels or proteinuria between the two groups. Infections occurred in 19% of the MMF group and in 33% of the CS+CY/CS+AZA group (p=0.29). The frequency of relapse was 15% and 11% respectively. Although it seems from the results of this study that CS+MMF is as effective as CS+CY/CS+AZA and with fewer side effects, an editorial in the same volume expresses the need for caution in the general application of the results of the study to large groups of patients with diffuse proliferative lupus nephritis (28). The doubts expressed seem to be related to the fact that the group of patients studied had good prognostic indicators and that the method protocol did not determine the total duration of the therapy. In a recent retrospective analysis we show that patients with proliferative lupus nephritis who expressed either toxicity or no response to CY, responded very well when switched to MMF while 6 patients with membranous lupus nephritis had no response to MMF (29).

Apart from the above, there are other clinical trials in progress for the assessment of more therapeutic protocols, but also for new therapeutic drugs and biological agents. One of these is LJP394, a small molecule synthesized from a polysaccharide base, joined to four DNA polymers. In a recent multicentre randomized trial it was found that this substance reduced the levels of anti DNA antibodies but did not protect from relapse of lupus nephritis. The monoclonal antibody anti CD40 ligand which prevents the communication between B and T lymphocytes, is under assessment in patients with severe nephritis in an ongoing comparative randomized study. Bindarit, an imidazole molecule which blocks the production of MCP-1, is programmed for administration as part of a comparative randomized study in the USA and in Europe. Also under way are other studies for the assessment of the place of MMF and of AZA. In addition plasmapheresis does not seem to be included in the standard forms of treatment [4] while the situation in regard o cyclosporin in the treatment of hyerplastic lupus nephritis is rather theoretical in the absence of suitable studies at present.

In conclusion, in the assessment of present or prospective therapies for severe lupus nephritis, the significantly inproved prognosis of patients with SLE who reach end stage renal failure must be taken into account. Apart from haemodialysis and peritoneal dialysis, renal transplantation constitutes a good alternative choice for patients with SLE with satisfactory survival figures for both patient and transplant (29).

References

1. Cervera R, Khamashta M, Font J. Systemic lupus erythematosus: Clinical and immunologic patterns of disease expression in a cohort of 1000 patients. Medicine 1993. 72: 113-124
2. Wallace DJ. The clinical presentation of SLE. In: Wallaaaace DJ, Hahn BH (eds) Dubois' Lupus Erythematosus. Lea and Febiger, Philadelphia, 1993: 317-321
3. Gladman DD. Prognosis and treatment of systemic lupus erythematosus. Curr Opin Rheumatol 1995, 7:402-408
4. Lewis EJ, Hunsicher LG, Lan S-P, Rohde RD, Lachin JM, for the Lupus Nephritis Collaborative Study Group. A controlled trial of plasmapheresis therapy in severe lupus nephritis. The lupus Nephritis Collaborative Study Group. N Engl J Med 1992, 326: 1373-1379
5. McCluskey RT. Lupus nephritis. In : Summers SC (ed) Kidney Pathology (decennia). AppletonCentyry Croffts, New York, 1975: 456-459
6. Churg J. Lupus nephritis In : Churg J. Bernstein J, Glassock RJ (eds). Renal diseases: classification and atlas of glomerular diseases. New-York, Igaku-Shoin, 1995: 151-157
7. Schwartz MM, Kawala KS, Korwin H, Lewis EJ. The prognosis of segmental glomerulonephritis in systemic lupus erythematosus. Kidney Int 1987, 32:274
8. Pollak VE, Pirani CL, Kark RM. Effect of large doses of prednisone on the renal lesions and life span of patients with lupus glomerulonephritis. J Lab Clin Med 1961, 57: 495-511
9. Szteinbok M, Stewart A, Diamond H, Kaplan D. Azathioprine in the treatment of systemic lupus erythematosus: a controlled trial. Arthritis Rheum 1971, 14:639-645
10. Ginzler E, Sharon E, Diamond H, Kaplan D. Long-term maintenance therapy with azathioprine in systemic lupus erythematosus. Arthritis Rheum 1975. 18 : 27-34
11. Hahn BH, Kantor OS, Osterland CK. Azathioprine plus prednisone compared with prednisone alone in the treatment of systemic lupus erythematosus : report of a prospective controlled trial in 24 patients. Ann Intern Med 1975, 83: 597-605
12. Decker JL, Klippel JH, Plotz PH, Steinberg AD. Cyclophosphamide or azathioprine in lupus glomerulonephritis : a controlled trial; results at 28 monts. Ann Intern Med 1975, 83:606-615
13. Cameron JS, Boulton-Jones M, Robinson R, Ogg C. Treatment of lupus nephritis with cyclophosphamide. Lancet 1979, ii:846-489
14. Feng PH, Jayaratnam FJ, Tock EPC, Seah CS. Cyclophosphamide in treatment of systemic lupus erythematosus: 7 years' experience. Br Med J 1973, 2: 450-452
15. Donadio JV Jr, Holley VE, Ferguson RH, llstrup DN. Progressive lupus glomerulonephritis treatment with prednisone and cyclophosphamide. Mayo Clin Proc 1976, 51: 484-494
16. Donadio JV JR, Holley VE, Ferguson RH, llstrup DN. Treatment of diffuse proliferative nephritis with prednisone and combined prednisone and cyclophosphamide. N Engl J Med 1978, 299: 1151-1155
17. Cameron JS. What is the role of long-term cytotoxic agents in the treatment of lupus nephritis? Nephrol 1993, 6: 172-176
18. Felson DT, Anderson J. Evidence for the superiority of immunosuppressive drugs and prednisone over prednisone alone in lupus nephritis. N.Engl J Med 1984, 311: 1528-1533
19. Balow JE, Austin HA, Muenz LR. Effect of treatment on the evolution of renal abnormalities in lupus nephritis. N. Engl J Med 1984, 311: 491-495
20. Austin HA, Klippel JH, Balow JE, LeRiche NG, Steinberg AD, Plotz PH et al. Therapy of lupus nephritis: controlled trial of prednisone and cytotocic drugs. N Engl J Med 1986, 314: 614-619
21. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum 1991, 34: 945-950
22. Boumpas DT. Austin HA. Vaughan EM. Klippel JH, Steinberg AD, Yarboro CH et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992, 320: 741-745
23. Bansal VK, Beto JA. Treatment of lupus nephritis: a meta-analysis of clinical trials. Am J Kidney Dis 1997, 29 : 193-1999
24. Klippel JH, Cyclophosphamide: ovarian and other toxicities. Lupus 1995, 4:1-2
25. Ioannidis JPA, Boki KA, Katsorida ME, Drosos AA, Skopouli FN, Boletis JN et al. Remission relapse and re-remission of proliferative lupus nephritis treated with cyclophosphamide. Kidney Int 2000, 57: 258-264
26. Boletis JN, Ioannidis JPA, Boki KA, Moutsopoulos HM. Intravenous immunoglobulin compared with cyclophosphamide for proliferative lupus nephritis. Lancet 1999, 3554:569-570
27. Chan TM, Li FK, Tang CSO, Wong RWS, Fang GX, Ji YL et al. Efficacy of mycophenolate mofetil in patients with diffuse prolifertive lupus nephritis. N. Engl J Med 2000, 343: 1156-1162
28. Falk RJ. Treatment of lupus nephritis – A work in progress N.Engl. J Med 2000, 34: 1182-1183
29. Kapitsinou PP, Boletis JN, Skopouli FN, Boki KA and Moutsopoulos HM. Lupus nephritis: treatment with mycophenolate mofetil, Rhemmatology 2003; 0: 1-4.
30. Ward MM. Outcomes of renal transplantation among patients with end stage renal disease caused by lupus nephritis. Kidney Int 2000, 57: 2136-2143