Treatment of Active Lupus Nephritis: Intravenous Immunoglobulin G Versus Cyclophosphamide or Azathioprine

D. Monova and S. Monov

Medical Institute – Ministry of the Interior, Department of Internal Disease, Clinic of Internal Disease and Therapy, Sofia, Bulgaria

Abstract

Backround. To evaluate the efficacy and safety of three therapeutic regimens: CYP – cyclophosphamide with intravenous methylprednisolone (i.v.MP), AZAP - azathioprine with intravenous methylprednisolone and IVIG – high doses intravenous immunoglobulin G as induction therapy in the patients with lupus nephritis (LN).

Methods. 132 patients with biopsy-proven LN were studied (48 in CYP, 23 in AZAP and 61 in IVIG group). 48 out of 132 received 1000 mg cyclophosphamide every 1 weeks for a total of 4 pulses, followed by 10 pulses every 3 months, while 23 started with 2 mg/kg/day azathioprine. The cyclophosphamide or azathioprine was combined with 1000 mg i.v.MP in three consecutive days. The cycle of four pulses was repeated after 3 months (total 12 pulses). Oral prednisolone was added after i.v.MP initially 2 mg/kg/every other day for 4 weeks and thereafter tapered by 10 mg every 2 weeks to a final dose of 10 mg every other day after 6 months. IVIG was applied once a day in dose of 85 mg/kg/24 h 3 times every other day. This course was undertaken after 1-3 months. In case of a relapse the induction therapy was repeated. The regimen was advised to continue for at least 2 more years.

Results. Full remission was observed in 26,52% patients and partial remission - in 31,82% patients. During the first 7 years of therapy, the cumulative incidence of partial or complete renal remission was not significantly different between the treatment groups. Renal relapses occur in 25% of LN patients and more often in the AZAP group. During follow-up 11,36% patients went into end-stage renal failure or died.

Conclusions. The efficacy of the induction therapy with cyclophosphamide or azathioprine and methylprednisolone is comparable with that of IVIG. IVIG appears to be a promising alternative for cyclophosphamide and azathioprine, especially in the LN patients with a strong will to conceive and with a high risk of premature ovarial failure and infections.

Key words: Lupus nephritis, intravenousimmunoglobulin G, cyclophosphamide, azathioprine

Introduction

The overall survival of patients with systemic lupus erythematosus (SLE) and glomerulonephritis has improved considerably over the last few decades (1). Although there is no consensus on outcome definitions, such as remission and relapse of lupus nephritis, most clinicians would agree on the following therapeutic goals for a patient with lupus nephritis (LN): to achieve prompt renal remission, to avoid renal flares and chronic renal impairment and fulfill these objectives with minimal toxicity. Although patient and renal survival rates have improved over the past decade, it should be stressed that current immunosuppressive regimens still achieve suboptimal results (2). Depending on how is it defined, a significant proportion (30-50% or higher) of patients with LN do not achieve complete remission despite treatment (3). Nevertheless, after 10 years of treatment, 5-10% of patients have died and further 5-15% have developed end-stage renal failure (4-5).

Failure to achieve a remission of the renal disease is associated with a significantly increased risk of end-stage renal failure, relapses, and death. The relapses are associated with an increased risk of developing end-stage renal failure, too (6). Any nephrologist who looks after patients with LN knows that the management of these patients remains a challenge. It has been also a source of real disagreement. The clinical presentations, histology, renal course, and responsiveness to treatment of LN are heterogeneous. Several questions remain unanswered, such as: the optimal therapy for inducing remission and the duration of treatment required, the optimal therapy for maintaining remission, and the best ways of treating relapses.

There is no convincing evidence that treatment of patients in remission actually improves their long-term prognosis (7).

Combined treatment with corticosteroids and cytotoxic immunosuppressive drugs is considered standart therapy in active LN. However, there is no consensus, whether cyclophosphamide (CY) or azathioprine (AZA) is the preferable drug (1). In the studies published until 1995, the results of treatment with azathioprine did not differ significantly from those obtained with cyclophosphamide containing regimens (8). We argued that intravenous methylprednisolone (i.v.MP) would more rapidly affect acute inflammation (9), while azathioprine would halt the progression of chronic lesions (10).

One of the main reasons to consider an alternative treatment for cyclophosphamide in the mostly young female lupus patients is the risk of infertility. Young women who eventually want to become pregnant will often choose a treatment option that is associated with better preservation of ovarian function even if the risk for renal relapse is grater (11). In recent years, other options, for example

Correspodence to: Daniela Valentinova Monova, Medical Institute – Ministry of the Interior, Department of Internal Disease, Clinic of Internal Disease and Therapy, 24 Veliko Turnovo st., Sofia 1504, Bulgaria; Tel.: ++35928437705; Fax.: +35929803649; E-mail:dmonova@abv.bg

mycophenolate mofetil, high doses intravenous immunoglobulin, have become available and are currently elevated in clinical studies. At the time we started this study in 1995, the combination of prednisone and cyclophosphamide intravenously was accepted as the standard treatment for patients with proliferative lupus nephritis (1). In our study we compare the efficacy of cyclophosphamide pulses and i.v.MP (CYP) with azathioprine and i.v.MP (AZAP), and with intravenous immunoglobulin G (IVIG) as induction therapy for lupus nephritis.

The intention of our study was to shed more light on high doses intravenous immunoglobulin G as a valuable alternative for cyclophosphamide or azathioprine. Our paper reports on the results in 132 patients with biopsy-proven LN with a minimum follow up of 5 years, and a median follow-up of 7,6 years.

Patients and methods

All study patients met the following criteria: the presence of minimum 4 American College of Rheumatology criteria for SLE (12), age 18 to 60 years, creatinine clearance (Cockcroft-Cault) > 25 ml/min and biopsy-proven lupus nephritis. All biopsies were reviewed and classified by a single nephropathologist, according to the 1995 WHO criteria (13) and activity and chronicity indices were scored (14).

Each patient was examined as follows: complete history, physical examination, review of systems, routine chemical analysis, urinalysis, renal function examination including creatinine clearance and additional tests, where necessary, measurement of complements (C3 and C4), circulating immune complexes and autoantibodies (anti-DNA, antinuclear and others if needed). A Phenotype analysis of peripheral blood mononuclear cells was performed by monoclonal antibodies: OKT3, OKT4, OKT8 and OKT7 (Ortho Diagnostic, USA). All measurements were performed by central laboratory using standard procedures. The immunological determinations were performed in a non-routine research laboratory. The patients were divided into three treatment groups (Table 1).

Table 1. Baseline characteristics of patients with lupus nephritis

Characteristics	CYP (n=48)	AZAP (n=23)	IVIG (n=61)
Female gender	43 (89, 58 %)	20 (86,96 %)	54 (88,52 %)
Age (years)	18-56 (28,4±10,2)	19-48 (30,6±7,4)	18-50 (29,6±8,7)
Age at diagnosis of lupus (years)	18-48 (22,7±8,7)	18-41 (23,5±6,1)	18-43 (24,2±7,4)
Hypertension (patients)	39 (81,25 %)	18 (78,26 %)	51 (83,61 %)
SLEDAI	28,6 (15-55)	23,1 (16-57)	29,2 (15-64)
Biopsy parameters			
WHO-class I (Minimal mesangial lupus nephritis)	2	1	4
WHO-class II (Mesangial proliferative lupus nephritis)	4	2	8
WHO-class III (Focal lupus nephritis)	2	1	5
WHO-class IV (Diffuse lupus nephritis)	26	14	32
WHO-class V (Membranous lupus nephritis)	14	5	12
Activity index	9,6 (7,8-11,5)	9,3 (6,1-11,2)	9,7 (7,5-11,8)
Chronicity index	2,5 (1,9-3,5)	2,1 (1,7-3,2)	2,7 (1,9-3,8)
Laboratory parameters			
Serum creatinine (μmol/l)	123,4 (98-262)	114,4 (102-248)	128,7 (108 – 304)
Proteinuria (g/24h)	5,3 (2,6-11,2)	4,9 (2,9-8,8)	6,4 (3,7-10,4)
Haemoglobin (g/l)	97 ± 5,4	104 ± 3,8	99 ± 4,9
ANA (titer)	876±834 (80-3200)	764±626 (80-2560)	928±786 (80-2560)
Anti-dsDNA (titer)	764±302	698±284	735±314
Complement C3 (g/l)	0,58±0,34	0,62±0,45	0,64±0,48

Abbreviations: AZAP - group treated with azathioprine/methylprednisolone/prednisone, CYP - group treated with cyclophosphamide/ methylprednisolone/prednisone, IVIG – group treated with high doses intravenous immunoglobulin G; SLEDAI - SLE disease activity index, WHO - World Health Organization

Patients in the CYP group received cyclophosphamide (1000 mg) every 1 weeks for a total of four pulses, followed by 10 pulses every 3 months. Protection of the bladder was accomplished by hyperhydratation (at least 1000 ml saline/glucose in 8 h). Patients in the AZAP group started with 2 mg/kg/day azathioprine. The cyclophosphamide or azathioprine was combined with i.v.MP (1000 mg) in three consecutive days. The cycle of four pulses was repeated after 3 months resulting in a total of 12 pulses. Oral prednisolone was added after i.v.MP initially 2 mg/kg/every other day for 4 weeks and thereafter tapered by 10 mg every 2 weeks to a final dose of 10 mg every other day after 6 months. The patients were followed at least monthly during the first 6 months and three-monthly from 6 months onwards. Each visit weight, blood pressure and current medication were recorded, and adverse events (including infections) were evaluated. In case of a relapse (doubling of the lowest obtained serum creatinine so far or/and development of either a nephrotic syndrome - proteinuria > 3,5 g/day and serum albumin < 30 g/l or proteinuria > 1,5 g/day without other

causes in a previously nonproteinuric patient) the induction therapy was repeated. In case of a third relapse, the patient was also switched to other treatment. In case of an impaired renal function (creatinine clearance < 40 ml/min) the cyclophosphamide dose was adjusted to 500 mg. If one week after the administration of cyclophosphamide, the white blood cells (WBC) were < $2,0x10^9$/l and/or platelet count was $100x10^9$/l, 75% of the initial cyclophosphamide dose was given consequently. If cytopenia ensued again (WBC < $1,5x10^9$/l), the patient continued treatment with IVIG.

IVIG was applied once a day in a dose of 85 mg/kg/24 h 3 times every other day. Depending on the clinical improvement afterwards this course could have been undertaken after 1-3 months resulting in total of 12 courses.(15)

When during azathioprine treatment white blood cell count was between 3,0 and $3,5x10^9$/l, the dosage was halved. It was discontinued and patient continued treatment with IVIG if white blood cell count dropped below $3,0x10^9$/l and/or platelets count was < $100x10^9$/l. Recommendations for the treatment of hypertension were given, but the choice of drugs was left to the physician. The prescription of ACE-inhibitors was compulsory.

The results of therapy were evaluated by clinical and laboratory data. The criteria for full or partial remission were as follows:

Full remission - unchanged or improved renal function, disappearance of edema and other clinical manifestations, returning of the values of haemoglobin, serum proteins and albumin to normal ranges, proteinuria < 0,5 g/24 h.

Partial remission – unchanged or improved renal function, improved clinical signs of the nephrotic syndrome only, without full normalisation of the laboratory data (proteinuria > 0,5 g/24 h, but < 1,5 g/24 h).

No effect - deterioration of renal function and/or persisting of nephrotic syndrome.

For patients in full or partial remission, the relapse of glomerulonephritis was suspected when there was doubling of the lowest obtained serum creatinine and/or a significant and progressive increase of proteinuria (>1 g/24 h for patients in full remission) or > 1g/24 h in excess of the baseline for patients in partial remission with or without abnormalities in urinary sediment and serum creatinine.

All data were analysed on an intention-to-treat basis using SPSS 13.0.1. Descriptive statistics included frequency tables of patients characteristics and baseline variables. A P-value < 0,05 was regarded statistically significant, on a two tailed level.

Data are expressed as mean values ± SD (standard deviation). Differences in laboratory findings between groups were assessed by means of Mann-Whitney rank sum test.

Results and discussion

The baseline characteristics of the 132 patients (15 male and 117 female) are shown in Table 1. 48 patients were included in the cyclophosphamide/ methylprednisolone group (CYP), 23 in the azathioprine/methylprednisolone group (AZAP) and 61 in the high doses intravenous immunoglobulin (IVIG) group. Of the 132 patients, 52 (39,39%) presented with renal impairment (estimated creatinine clearance according to Cockcroft and Gault < 80 ml/min) (16), 118 (89,39%) were nephrotic (proteinuria > 3,5 g/24 h) and in 78 patients (59,09%) nephritis was the presenting symptom of SLE. The baseline parameters between the various treatment groups did not differ significantly. There were no significant differences in WHO-classification or in the activity and chronicity indexes between the treatment groups.

The final outcome for the various treatment related events is summarized in the Table 2.

Table 2. Outcome at last follow-up

Parameter	CYP (n=48)	AZAP (n=23)	IVIG (n=61)
Follow-up	7,4 years	7,7 years	8,5 years
Complete remission	12 patients (25%)	6 patients (26,09%)	17 patients (27,87%)
Partial remission	16 patients (33,33%)	7 patients (30,43%)	19 patients (31,18%)
SLEDAI	5,6 (0-8)	5,1 (0-10)	4,2 (0-8)
Renal relapse (n)	26 in 12 patients	16 in 8 patients	23 in 15 patients
Doubling of serum creatinine	12 patients (25 %)	6 patients (26,09%)	14 patients (22,95%)
ESRD or died	5 patients (10,42 %)	3 patients (13,04 %)	7 patients (11,48%)
Serum creatinine (μmol/l)	84,4±67,9	80,7±59,8	78,7±78,6
Proteinuria (g/24h)	0,5 (0,0-2,2)	0,7 (0,0-1,9)	0,4 (0,0-1,3)
Haemoglobin (g/l)	118 ± 1,6	120 ± 1,9	124 ± 2,6
ANA (titer)	148±56 (40-320)	154±66 (40-320)	135±78 (40-640)
Anti-dsDNA (titer)	104±32	97±24	89±28
Complement C3 (g/l)	0,58±0,34	0,62±0,45	0,64±0,48

According to the above-mentioned criteria full remission was observed in 35 (26,52%) patients and partial remission - in 42 (31,82%) patients. During the mean 7,6 years of therapy, the cumulative incidence of partial or complete renal remission (58,33% in CYP group, 56,52% in AZAP group and 59,02% in IVIG group) was not significantly different between the treatment groups, suggesting that the efficacy of the induction therapy with CYP or AZAP is comparable with that of IVIG. However, after a median follow-up of 7,6 years, we observed relapses in all groups.

Renal relapses occur in 33 (25%) of LN patients and more often in the AZAP group (69,56% of the patients). There were no significantly differences in the activity or chronicity indexes in renal biopsies between patients who experienced a relapse compared to those who did not. During the follow-up 15 (11,36%) patients went into end-stage renal disease

(ESRD) or died (7 of them of a non renal cause): 5 in the CYP group (10,42%), 3 in the AZAP group (13,04%) and 7 in IVIG group (11,48%).

Serum creatinine and proteinuria decreased in most patients (64,39%), indicating that the relapses could be treated effectively so far. This is in line with the observation that at last visit, the median serum creatinine and proteinuria were 84,4 µmol/l and 0,6 g/24 h in the CYP group, 80,7 µmol/l and 0,7 g/24 h in the AZAP group, and 78,7 µmol/l and 0,4 g/24 h in the IVIG group, respectively.

Serum creatinine significantly decreased in treatment groups compared to pretreatment values ($P < 0,001$). The levels of anti-double-stranded DNA antibodies (anti-dsDNA) and antinuclear antibodies (ANA) decreased rapidly without significant differences between the groups (Table 2). The SLE Disease Activity Index did not differ between the treatment groups, be it a significantly decreased parameter. The serum levels of complement C3 and complement C4 returned to normal levels.

Table 3. Main adverse events

Parameter	**CYP** (n=48, 5 m, 43 f)	**AZAP** (n=23, 3 m, 20f)	**IVIG** (n=61, 7 m, 54 f)
Infections	16 patients (33,33 %)	5 patients (21,74 %)	2 patients (3,28 %)
WBC < $2,0.10^9$/l	20 patients (43,75 %)	11 patients (43,47%)	0
Amenorrhea	11 f (25,58%)	3 f (15%)	0
Osteoporosis	2 (4,17%)	1 (4,35%)	0

Looking at the main adverse events (Table 3) we had infections in 23 patients (17,42%) and amenorrhea - in 14 (11,11%) female patients. In IVIG treatment group the adverse events were significantly lower compared with the CYP or AZAP groups. Recently, Houssiau et al. reported the results of a controlled Euro lupus trial where patients were given an induction therapy with three i.v.MP pulses and high (1 g every month for eight months) or low (0,5 g every forth night for a total of 3 g) dose of intravenous cyclophosphamide. Azathioprine was used as maintenance. They found that severe infections were doubled in the patients who received high-dose cyclophosphamide but the difference was not statistically significant. Renal failure, death, renal flares, renal remission and treatment failure were similar in the two groups of patients (17).

The observed incidence of doubling of serum creatinine in our treatment groups was less than 25%, after a mean follow-up of 7,6 years. There was no significant difference between treatment groups in the proportion of patients who developed a doubling of their serum creatinine. The overall treatment result was better than we had presumed at the start of the study. Even better than expected overall treatment results might have been due to the fact that most of the patients were treated with long-term maintenance therapy and that in the last decades patients known to have lupus are referred earlier for renal biopsy and as a consequence an earlier immunosuppressive treatment is start.

Conclusion

In conclusion, in our patients groups, IVIG therapy was superior to azathioprine/methylprednisolone or cyclophos-phamide/methylprednisolone with regard to relapses (21,31% in IVIG group vs 25% in CYP group, and vs 34,48% in AZAP group) and short-term infections. However, so far renal function at last visit did not significantly differ between the groups. IVIG appears to be a promising alternative for cyclophosphamide and azathioprine, especially in the patients with a strong will to conceive and with a high risk of premature ovarial failure and infections.

Optimal management of LN remains a challenge because of the heterogeneity of the disease at presentation and its unpredictable course (18). Flexible strategies, aggressive for induction and with low dosing in quiescent phases may reduce the side effects but requires expertise and strict clinical and biological surveillance. IVIG may be safe and effective therapeutic options for patients with active lupus glomerulonephritis and may be recommended predominantly in female lupus nephritis populations and in patients, unresponsive to aggressive conventional treatment. Large multicenter studies are needed to gather enough patients to test our hypotheses, keeping in mind that very long-term follow-up is required before conclusions on mortality and ESRD rates can be drawn.

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