# What happens after complete withdrawal of therapy in patients with lupus nephritis

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**ABSTRACT**

**Objective.** *Whether and when is it possible to completely stop immunosuppression in patients with lupus nephritis is still poorly defined.*

**Methods.** *An attempt to slowly and progressively eliminate steroids and immunosuppressive drugs was tried in 73 of 161 (45.3%) patients with lupus nephritis who achieved a stable clinical remission defined as normal serum creatinine, proteinuria <0.5g/24h, inactive urine sediment, and no clinical signs of extra-renal activity of SLE for at least 12 months.*

**Results.** *Twenty-one out of the 73 patients (28.7%) who met the criteria for withdrawal of treatment developed flares during the phase of progressive reduction of therapy and their treatment was reinforced. Twenty patients entered remission again; the last patient was lost to follow-up at achievement of partial remission.*

*In the other 52 of the 73 patients (71.2%), it was possible to completely withdraw treatment. Of these, 32 patients (group A) did not resume therapy for the subsequent follow-up (median 101.8 months); the other 20 patients (group B) had at least one flare, in median 37 months after withdrawing therapy, and had to be retreated. At the last observation, after a median follow-up of 286 months, 10 of these 20 patients were off therapy. At the last observation, two patients in group A and two in group B had died, no patient of group A and two of group B had developed renal insufficiency (serum creatinine 2.5 and 3 mg/dl, respectively).*

*Compared to patients in group B, group A patients received longer treatment (98.1 vs. 31.0 months; p=0.01), had longer remission (52.8 vs. 12.0 months; p=0.000) before withdrawal of therapy, and continued chloroquine after stopping therapy (52% vs. 10%; p=0.004).*

*In comparison to patients who never stopped therapy, patients who were able to interrupt treatment had lower risk of chronic renal insufficiency (3.8% vs. 28.4%; p=0.000), end-stage renal disease (0 vs. 12.8%; p=0.01), arterial hypertension (32.7% vs. 66.9%; p=0.000) and cardiovascular events (11.5% vs. 27.5%; p=0.04).*

**Conclusion.** *Complete withdrawal of therapy is feasible in selected patients who achieved stable remission after long-term treatment. The reduction of treatment must be done in a very gradual manner, progressively and under strict medical surveillance. The withdrawal of therapy allows the patients to reduce renal and extra-renal damage accrual. Treatment with chloroquine may help to maintain remission in patients who discontinue steroids and immunosuppressive drugs.*

## Introduction

The current therapeutic approach in patients with lupus nephritis (LN) consists of an induction treatment aimed at quenching the activity of the disease, and in a maintenance regimen aimed to prevent flares of activity and the silent progression of the disease while minimising iatrogenic adverse events. This treatment rests on a combination of intravenous methylprednisolone pulses followed by high-dose prednisone, associated with cyclophosphamide, administered intravenously or orally, or mycophenolate mofetil (MMF) (1). In aggressive or resistant cases rituximab may be added (1, 2). A number of meta-analyses of the randomised controlled trials that compared cyclophosphamide with MMF in patients with proliferative LN showed that MMF is as effective as cyclophosphamide in achieving remission in LN. The risk of amenorrhoea, leukopenia, and alopecia is lower, while the risk of diarrhoea is higher with MMF (3-5).

For maintenance, steroids are associated with low-dose azathioprine, MMF, or cyclosporine (2-6). A promising

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drug that may be used for maintenance treatment is Belimumab, a monoclonal antibody directed against the B-lymphocyte stimulator (BLyS) and its receptors on B-cell subsets. This drug has been recently approved by the Food and Drug Administration, but little information is available on its long-term use (7).

In recent years the doses of corticosteroids have been reduced and in a few patients the use of rituximab has made it possible to completely stop prednisone (8, 9). However, in spite of the less toxic regimens used today, many patients with LN still suffer from a number of adverse events caused by treatment such as infection, cardiovascular disease, metabolic syndrome, osteoporosis, diabetes, etc. These iatrogenic complications not only can impair the quality of life but are also responsible of severe morbidity and mortality. In response to a questionnaire, some physicians who treat LN patients stated that they attempted to discontinue corticosteroids (10). However, most patients are still given low-dose prednisone or other immunosuppressive drugs indefinitely, and no guidelines are available about the possibility of completely discontinuing immunosuppression in patients with LN.

Years ago, we tried to completely stop corticosteroids and immunosuppressive drugs in patients with quiescent LN (11). Reactivation of lupus occurred only in some patients but many patients did not show any activity of lupus and are still enjoying a normal life without treatment after many years. On the basis of these initially good results, we have decided to continue this policy and report here our cumulative experience with withdrawal of treatment in patients with LN.

## Methods

*Participants*

One hundred and sixty-one patients were considered in this study. All patients had a diagnosis of LN and were followed by our Unit for at least 5 years. Two patients were Hispanics, all the others were Caucasians. All patients fit the diagnosis of SLE according to the American College of Rheumatology criteria (12). In 6 patients the diagnosis of LN was established on clinical grounds, in the other 155 patients the diagnosis relied on renal biopsy. For the aims of this study, renal biopsies were reclassified according to the classification made by the International Society of Nephrology and the Renal Pathology Society (13). Activity and chronicity indices were calculated according to Austin *et al*. (14).

*Induction and maintenance treatment*

Patients with class III, IV, V plus III, or IV received an induction therapy with either of these schedules (15): I) Three consecutive methylprednisolone pulses (MPP) 0.5–1g each according to the body weight of the subject (<or >50 kg), followed by oral prednisone (0.5 to 1 mg/kg/day according to the severity of nephritis) for 1–2 months then gradually tapered to a maintenance dosage. II) Oral prednisone 1-2 mg/kg day for 1–2 months then gradually tapered. In the most severe cases in both schedules I and II corticosteroids were associated with cyclophosphamide (1.5–2 mg/kg/day) or chlorambucil 0.1-0.2 mg/kg/day for 2-3 months or with azathioprine 2mg/kg day for 6–12 months.

For maintenance therapy, prednisone was gradually tapered to 10–15 mg per day, and in some cases azathioprine (1–2 mg/kg/day), or MMF (1–2 g per day), or cyclosporine (3 mg/kd per day) were added. Patients with pure lupus membranous nephritis either received the same treatment used for proliferative lupus nephritis or a 6-month treatment alternating monthly corticosteroids and a cytotoxic agent, a regimen similar to that we are adopting in idiopathic membranous nephropathy (16).

Lupus flares were treated with the same schedules used for induction therapy.

*Definitions*

According to the Renal Disease Subcommittee of the American College of Rheumatology (17), we used the following definitions:

- Complete renal remission: serum creatinine ≤1.2mg/dL, and 25% increase of baseline creatinine clearance if abnormal, proteinuria <0.2g/24h, and inactive sediment.
- Partial renal remission: proteinuria from 0.21 to 2 g/day and serum creatinine ≤1.2 mg/dL, and 25% increase of baseline creatinine clearance if abnormal.
- Chronic renal insufficiency (CRI): doubling of plasma creatinine lasting for at least 6 months with plasma creatinine >2mg/dL and creatinine clearance ≤40ml/min.
- End-stage renal disease: the need of dialysis.
- Renal flares were subdivided into nephritic flares and proteinuric flares and defined as previously reported (18).

*Withdrawal of treatment*

In all patients with normal serum creatinine, proteinuria ≤0.5g/24h, inactive urine sediment, and no clinical signs of extra-renal activity of SLE for at least 12 months, a progressive reduction of therapy was attempted. In the majority of the cases, we started to reduce the dosage of immunosuppressive drugs, by halving the dose of MMF, azathioprine, or cyclosporine. After complete elimination of the immunosuppressive drugs, corticosteroids were maintained stable for a 2–3 months and then were halved every 2–3 months until complete withdrawal. Patients who were treated with hydroxychloroquine, antihypertensive drugs, statins or other supportive therapies continued the treatment. Patients were frequently monitored during the period of dose reduction. After complete withdrawal of immunosuppressive and steroid agents, patients were seen every 15 days for the first 2 months, every month for 6 months, and then every 2–3 months. At the follow-up visit, patients were always seen by a nephrologist and the following tests were performed: serum creatinine, blood urea, serum electrolytes, serum C3 and C4, anti-dsDNA antibodies, urinalysis with measurement of 24 hours proteinuria, and interpretation of urine sediment.

*Statistical analysis*

Since the distribution of the variables showed high non-normality, the median and 2 5 $^{th}$ –75$^{th}$ interquartile ranges (IQR) were used for descriptive analysis. T-test and the non-parametric Wilcoxon-test were used to investigate

differences between the two groups of patients. Cross-tabulated data were analysed by Chi-square test, or by Fisher's test when the expected cell count was less than five.

## Results

Of 161 patients with LN of class III, IV or V or mixed forms followed in our Unit for at least 5 years from the diagnosis of LN, 73 met the criteria for withdrawal of treatment. Twenty-one out of these 73 patients (28.7%) developed flares during the phase of progressive reduction of therapy. Of these flares 4 were extrarenal, 2 nephritic, 15 proteinuric. The flares occurred while patients were receiving only low doses of prednisone (from 0.05 to 0.07 mg/kg/day). Flares were treated according to the protocols used for induction therapy. Twenty patients entered remission again. At the end of a median follow-up of 164 months (range 98–285 months) from the diagnosis of LN, two patients had chronic renal dysfunction (serum creatinine1.7 and 1.9 mg/dl, respectively), 4 patients had non-nephrotic proteinuria and the other 14 patients were in complete remission. In the last patient, serum creatinine increased from 0.8 mg/dl to 3.2 mg/dl and proteinuria from 0 to 5.2 g/day when she was taking 2.5 mg per day of oral prednisone. She received three MPP and oral cyclophosphamide. Three months later, her serum creatinine was 1.4 mg/dl and proteinuria 1 g per day, but she developed diabetes requiring insulin therapy. The patient was lost to follow-up.

In the other 52 patients it was possible to completely withdraw treatment. There were no significant differences in the clinical and histological characteristics at presentation and in type of induction therapy between patients who were able to stop therapy and those who were not, with the exception of a higher activity index (8 *vs*. 6; $p$=0.04) and more frequent achievement of remission (100% *vs*. 78%; $p$=0.007) in those who stopped therapy (Table I).

**Table I.** Comparison between patients with lupus nephritis who never stopped therapy (109 patients) and those who were able to stop therapy (52 patients) in the clinical, histological characteristics at presentation, treatment and outcome of lupus nephritis. If not differently specified, numbers refer to the median and ($25^{th}$ –$75^{th}$ interquartile ranges).

| | No stop therapy: 109 patients | Stop therapy: 52 patients | *p*-value |
|---|---|---|---|
| Age years | 29.7 (23-33.4) | 30.4 (24-34.4) | ns |
| Female: number of patients | 99 (91%) | 48 (92%) | ns |
| Months from diagnosis of SLE to LN | 0 (0-26.02) | 1,02 (0-20.8) | ns |
| Serum creatinine mg/dl | 0.9 (0.7-1.4) | 1.08 (0.8-1.53) | ns |
| Renal insufficiency: number of patients | 35 (32%) | 22 (42%) | ns |
| Proteinuria g/day | 3.3 (1.95-5.2) | 3.9 (1.8-5) | ns |
| Nephrotic syndrome: number of patients | 51 (46%) | 27 (52%) | ns |
| Number urinary erythrocytes/high power field | 15 (5-40) | 15 (5-40) | ns |
| Class III/ IV/V/III+V/IV+V/NA | | | |
| Number of patients | 16/46/29/5/10/3 | 7/30/7/4/1/3 | ns |
| Activity index | 6 (2-8) | 8 ( 3-11) | 0.04 |
| Chronicity index | 2 (1-3) | 2 (0-3) | ns |
| C3 <90mg/dl: number of patients | 91 (83.5%) | 45 (86.5%) | ns |
| C4 < 20mg/dl: number of patients | 88 (81%) | 38 (73%) | ns |
| Methylprenisolone Pulses: number of patients | 73 (67%) | 42 (81%) | ns |
| Cyclophosphamide/Chlorambucil/Azathioprine induction therapy: number of patients | 82 (75.2%) | 41 (78.8%) | ns |
| Complete remission: number of patients | 85 (78%) | 52 (100%) | 0.007 |
| Follow-up months | 175 (110-259) | 268 (183-348) | 0.000 |

**Table II.** Clinical, histological characteristics at presentation and therapy of the 52 patients who stopped therapy divided in Group A (patients who never resumed therapy) and in Group B (patients who had to be retreated). If not differently specified, numbers refer to the median and ($2\,5^{th}$ -$75^{th}$ interquartile ranges).

| | Group A 32 patients | Group B 20 patients | *p*-value |
|---|---|---|---|
| Age years | 30.7 (24.4-34.4) | 30,4 (23.4-33.8) | ns |
| Female: number of patients | 30 (91%) | 18 (90%) | ns |
| Months from diagnosis of SLE to LN | 0.51 (0-23.8) | 1.02 (0-19.3) | ns |
| Class III/IV/V/III+V/IV+V/NA | | | |
| Number of patients | 4/16/7/1/1/3 | 3/14/0/3/0/0 | ns* |
| Activity index | 7 (3-11) | 8 (6-12) | ns |
| Chronicity index | 2 (0-3.25) | 1 (0.25-2.75) | ns |
| Serum creatinine mg/dl | 0.9 (0.8-1.43) | 1.26 (0.9-1.8) | ns |
| Renal insufficiency: number of patients | 12 (37.5%) | 10 (50%) | ns |
| Proteinuria g/24h | 2.77 (1.2-4.7) | 4.75 (2.75-6.33) | 0.04 |
| Nephrotic syndrome: number of patients | 14 (43.7%) | 12 (40%) | ns |
| Number urinary erythrocytes/high power field | 20 (5-40) | 15 (6-40) | ns |
| C3 <90 mg/dl: number of patients | 26 (81%) | 19 (95%) | ns |
| C4 <20 mg/dl: number of patients | 23 (72%) | 15 (75%) | ns |
| Hypertension: number of patients | 14 (44%) | 14 (70%) | ns |
| Cyclophosphamide/Chlorambucil/Azathioprine: induction therapy: number of patients | 27 (84.3%) | 13 (65.5%) | ns |
| Methylprednisolone pulses: Number of patients | 25 (78%) | 17 (85%) | ns |
| Cytotoxic therapy maintenance: number of patients | 20 (62.5%) | 5 (25%) | 0.019 |

*$p$=0.06 for Class V group A *vs*. group B.

## Outcome after stopping therapy

Therapy was stopped in 52 patients, in median 73 months (31.5–125) after the beginning of induction therapy for LN. After therapy was withdrawn patients were followed for a median of 172 months (88–292). Patients were divided into two groups. Group A included 32 patients who never had any renal or extra-renal flare of lupus activity during a median follow-up of 101.8 months (44–180) after interruption of treatment. Group B included 20 patients who had at least one flare-up after treatment

withdrawal. The median follow-up after interruption of treatment in group B was 286 months (183–312). Altogether 20% of our cohort (32 out of 161) were able to stop therapy until the end of the follow-up and another 12% of patients (20 out of 161) stopped therapy for one part of the observation.

At diagnosis of LN the only significant differences between group A and Group B were higher proteinuria (4.75 *vs*. 2.77g/day; $p$=0.04) and less frequent use of cytotoxic drugs in addition to steroids for maintenance therapy (25% *vs*. 62.5%; $p$=0.019) in patients of group B (Table II). At withdrawal of therapy there was no difference between patients of the two groups as far as renal function, proteinuria, immunological parameters, and previous occurrence of flares was concerned. Seventeen patients (53%) of group A and 2 patients (10%) of group B were treated with chloroquine before and after withdrawal of therapy ($p$=0.004). However, the duration of treatment (from start of treatment to withdrawal of therapy 98.1 *vs*. 31 months; $p$<0.01), and duration of remission (from first remission to therapy withdrawal 52.8 *vs*. 12.01months; $p$=0.000) were significantly longer in group A than in group B (Table III).

Patients in group B developed flares in median 37 months (20–77) after stopping therapy, 10 were proteinuric flares, 5 nephritic flares and 5 extra-renal flares. All of them restarted therapy and their outcome is reported in Figure 1. At the last follow-up visit 286 months (183–312) after first stopping therapy 10 patients in group B were without treatment while the remaining 10 patients received low-dose prednisone (from 2.5 to 7.5 mg/day) associated with MMF in 2 patients.

Altogether the 20 group B patients received no therapy for 172.53 out of their 442.49 cumulative years (40.8%) of follow-up.

Considering the number of flares that group B patients developed before and after the interruption of treatment no difference was found either in the rate of nephritic flares (0.006 /patient/years *vs*. 0.005 patient/years) or in proteinuric flares (0.002 patient/years *vs*. 0.001 patient/years).

**Table III.** Comparison of the characteristics at stop therapy between patients of Group A (patients who never resumed therapy) and patients of Group B (patients who had to be retreated). If not differently specified, numbers refer to the median and (25$^{th}$–75$^{th}$ interquartile ranges).

| | Group A 32 patients | Group B 20 patients | $p$-value |
|---|---|---|---|
| Ser. Creatinine mg/dl mean±SD | 0.8 ± 0.26 | 0.92 ± 0.25 | ns |
| | 0.8 (0.7-0.93) | 0.9 (0.8-1) | |
| Proteinuria g/24h mean±SD | 0.26 ± 0.29 | 0.47 ± 0.59 | ns |
| | 0.19 (0.05-0.3) | 0.21 (0.04-0.5) | |
| Positive Anti- DNA Ab | | | |
| Number of patients | 12 (37.5%) | 5 (25%) | ns |
| C3 <90 mg/dl: number of patients | 7 (21.8%) | 7 (35%) | ns |
| C4 < 20 mg/dl: number of patients | 10 (31%) | 6 (30%) | ns |
| Chloroquine therapy | | | |
| Number of patients | 17 (52%) | 2 (10%) | 0.004 |
| Prot flares: number of patients | 10 (31%) | 4 (20%) | ns |
| Nephritic flares: number of patients | 2 (6.2%) | 2 (10%) | ns |
| Months from start therapy to remission | 21.7 (10-35) | 12.1 (5.4-19.3) | 0.04 |
| Months from start therapy to stop therapy | 98.1 (53-136) | 31 (20-77) | 0.01 |
| Months from remission to stop therapy | 52.8 (22-86) | 12.01 (7-22) | 0.000 |

SD: standard deviation.

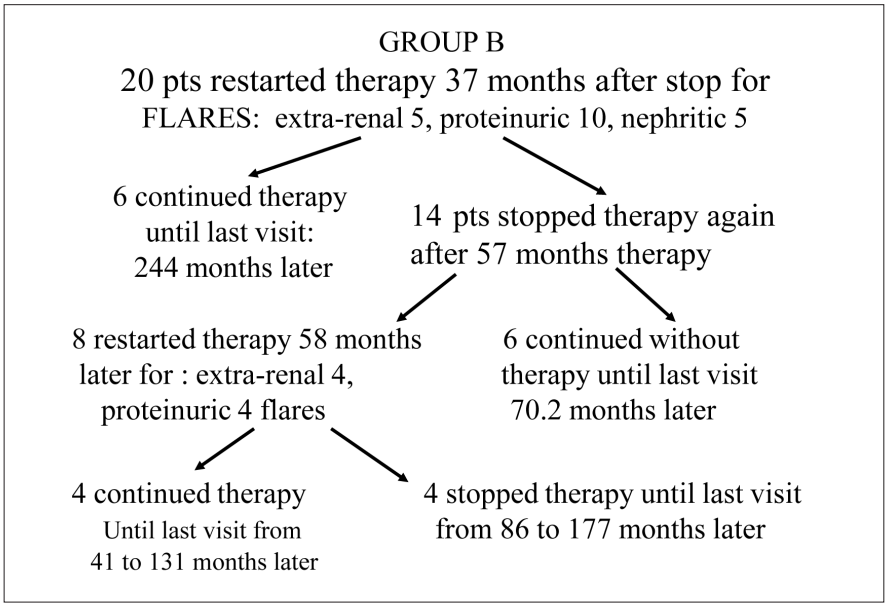


**Fig. 1.** Outcome of the 20 patients of group B after withdrawal of therapy.

**Clinical status at last observation (Table IV and V)**

The median time from the diagnosis of LN to the last follow-up visit was 192 months (151–350) in patients of group A and 311 months (265–348) in group B. The median serum creatinine (0.8 *vs*. 0.9 mg/dl) and proteinuria (0.08 *vs*. 0.13 g per day) were similar in the two groups (Table IV). No patient in group A had a doubling of serum creatinine *vs*. 2 patients in group B (serum creatinine respectively 2.5 and 3.0 mg/dl). No patient had to be treated with dialysis. There were 2 deaths per group (cardiac infarct and cerebral haemorrhage in group A, cardiac infarct and cancer in group B).

The outcome of patients who had treatment stopped was compared with that of patients who continued steroids and immunosuppressive agents (Table V). After a median follow-up of 268 months (183–348) for the 52 patients who stopped and 175 months (110–259) for 109 patients who continued therapy, there was no difference in deaths (7.6% *vs*. 10.1%). However,

**Table IV.** Clinical status at last observation of patients who stopped therapy divided in Group A (patients who never resumed therapy) and of Group B (patients who had to be re-treated). If not differently specified numbers refer to the median and ($25^{th}$–$75^{th}$ interquartile ranges).

| | Group A: 32 patients | Group B: 20 patients | *p*-value |
|---|---|---|---|
| Total follow-up months | 192 (151-350) | 311 (265-348) | 0.06 |
| Follow-up after first stop months | 101.8 (44-180) | 286 (183-312) | 0.00 |
| Serum creatinine mg/dl | 0.8 (0.7-0.96) | 0.9 (0.8-1.18) | ns |
| Proteinuria g/day | 0.08 (0.03-0.17 | 0.13 (0.08-0.35) | ns |
| Renal insufficiency | 0 | 2 (10%) | ns |
| Dialysis | 0 | 0 | |
| Deaths | 2 (6.2%) | 2 (10%) | ns |

**Table V.** Comparison between the clinical status at last observation of patients with lupus nephritis who never stopped therapy (109 patients) and those who were able to stop therapy (52 patients). If not differently specified numbers refer to the median and ($25^{th}$–$75^{th}$ interquartile ranges).

| | Stop therapy 52 pts Follow-up 269 months | No stop therapy 109 pts Follow-up 175 months | *p*-value 0.00 |
|---|---|---|---|
| Deaths number of patients | 4 (7.6%) | 11 (10.1%) | ns |
| Chronic renal insufficiency number of patients | 2 (3.8%) | 31 (28.4%) | 0.000 |
| Haemodialysis number of patients | 0 | 14 (12.8%) | 0.01 |
| Arterial hypertension number of patients | 17 (32.7%) | 73 (66.9%) | 0.000 |
| Cardiovascular accidents** number of patients | 6 (11.5%) | 30 (27.5%) | 0.04 |
| Cholesterol (mg/dl) | 219 (188-256) | 245 (191-265) | 0.01 |
| Triglyceride (mg/dl) | 110 (81-155) | 147 (96-178) | 0.0001 |

**Stop therapy patients: Myocardial infarct 3 patients, Cerebral thrombosis 3 patients.
No stop therapy patients : Myocardial infarct 8 patients, Cerebral thrombosis 15 patients, pheripherical arterial thrombosis 2 patients, transient ischaemic attack 5 patients.

the risks of chronic renal insufficiency (3.8% *vs*. 28.46%; $p<0.000$), end-stage renal disease (0 *vs*. 12.8%; $p<0.01$), and arterial hypertension (32.7% *vs*. 66.9% $p=0.000$) were significantly lower in patients who stopped therapy. Cardiovascular events occurred in 11.5% of patients who stopped *vs*. 27.5% of those who continued therapy ($p=0.04$). Also the median levels of serum cholesterol 219 (188–256) *vs*. 245(191–265) mg/dl; $p=0.01$) and triglycerides 110(81–155) *vs*. 147(96–178) mg/dl; $p=0.0001$) were significantly lower in patients who stopped treatment.

## Discussion

The prognosis of patients with LN has progressively improved over the years. Recently, new agents have been added to the therapeutic armamentarium for induction and maintenance therapies. It is hoped that in the near future, the use of newer agents and a better knowledge of the pharmacogenomics will make possible the personalisation of treatment, maximising the clinical benefit and minimising the adverse events (19). Today, however, the prolonged exposure to corticosteroids and other immunomodulating agents still represents a major cause of morbidity (20-23). This risk is even higher in patients with LN, an aggressive disease that requires a vigorous treatment.

For these reasons, the possibility of interrupting immunosuppressive treatment, definitively or transiently, is welcome. Attempts have been made in the past, but resulted in failure, with the development of severe lupus exacerbation and renal function impairment (24, 25). The development of flares was probably caused by a too a rapid discontinuation of therapy. Actually, a slower, progressive tapering of medications led to a complete withdrawal of therapy in our previous experience (11). Only a few papers have reported the results of discontinuation of therapy in patients with LN. Pablos *et al*. discontinued cyclophosphamide in 11 patients with class IV LN who reached complete remission. Four patients relapsed following therapy withdrawal (36%). Clinical remission with re-induction therapy could not be achieved in two patients. (26). Mosca *et al*. discontinued cyclophosphamide in 33 patients with diffuse proliferative LN previously treated with pulse steroids and a short course of pulse cyclophosphamide. Fifteen patients (45%) experienced a renal flare after the discontinuation of cyclophosphamide. Of these flares 24% occurred shortly after the discontinuation of therapy (early flares), while the other 21% occurred more than 2 years after treatment discontinuation (27). The only paper that reported the complete withdrawal of therapy including steroids is that of Euler *et al*. (28). In his paper 14 patients with severe SLE were treated with a protocol of plasmapheresis and high-dose pulse cyclophosphamide followed by 6 months of oral immunosuppression. Rapid improvement was achieved in all patients. Immunosuppressants, including corticosteroids, were withdrawn at month 6 in 12 patients. Eight patients (57%) continued without treatment for a mean period of 5.6 years.

During an attempt to discontinue treatment, the most delicate phase is the reduction of treatment. As pointed out by an excellent review by Grootsholden and Berden, the rate of lupus exacerbations in this phase may range between 8 and 16/100 patient/years (29). In our series, 21 patients (13% of the whole population in study) developed flares while the therapy was progressively reduced. Reinforcement of therapy obtained complete remission in all but one patient who achieved only partial remission and developed diabetes after the MPP. Eventually, we were able to completely stop treatment in 52 of 161 (32%) patients with LN. After interruption of treatment, 38% of these 52 patients had at least one flare. This incidence is similar to the 36% and 45% reported in other studies (26, 27, 28). However, in our patients interruption of

treatment was made after a median of 73 months of continuous therapy. This may explain why flares developed later, in median almost 3 years after withdrawal of treatment. Moreover, some patients who had flares could again stop treatment after the resolution of the flare, so that they spent around 40% of the follow-up without corticosteroids or other immunosuppressive drugs.

Patients who never had flares after withdrawal of therapy, after induction therapy, have received more frequently cytotoxic therapy in addition to steroids for maintenance than those who relapsed, 62.5 *vs*. 25%. This could have contributed in quenching the activity of the disease. As a matter of fact, the importance of maintenance cytotoxic therapy after induction in consolidating the remission is well known (30). The importance of late withdrawal may also be demonstrated by the fact that the median duration of treatment before its interruption was considerably longer in patients who did not develop any flare, 90 months *versus* 30. The duration of remission before withdrawal of therapy seems also to be important. Patients who never had flares have been in remission for a significantly longer period before withdrawal of therapy than those who had new flares. A significantly higher number of patients in group A were on chloroquine treatment before and after withdrawal of therapy than patients of group B. Antimalarial agents are part of the immunomodulatory regimen used to treat patients with SLE and may contribute in preventing exacerbations of lupus (31-33).

The benefits of stopping treatment are clearly demonstrated by the comparison with our patients who continued immunosuppression. Patients who stopped therapy had less frequently a doubling of serum creatinine and none developed ESRD. Obviously, patients who continued therapy had a more aggressive disease and this may account for these differences, although we cannot exclude that this worst outcome in some patients could be due to low compliance to therapy. Nevertheless, the levels of serum cholesterol and serum triglycerides were significantly lower in the group without treatment. More importantly, arterial hypertension and cardiovascular events were significantly less frequent in patients who stopped therapy. Again, in spite of lupus exacerbations, at the end of a long-term follow-up there was no difference in the clinical status between patients who maintained a stable remission and those who showed flares after interruption of treatment.

In conclusion, based on our experience, discontinuation of a "specific" therapy seems to be possible in patients who have entered a stable and prolonged remission. In our experience this is possible in around 1/3 of patients with lupus nephritis. Of them, 60% (*i.e*. 20% of the whole population in study) never started therapy again. However, discontinuation of therapy should attempted only in selected cases, *i.e*. patients who have received maintenance therapy for at least 5 years and who have been in complete renal remission for at least 3 years. To avoid severe and even irreversible renal failure, the dosage of drugs must be reduced in a very gradual manner. The tapering before complete discontinuation may require many months and must be done under strict surveillance. If these recommendations are observed, the complete withdrawal of treatment is safe and may prevent the burden of continuous immunosuppression and drug-related side effects. A multicentre randomised controlled trial is necessary to confirm these results.

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