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Discontinuation of immunosuppression in proliferative lupus nephritis: is it possible?

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Introduction

The search for an optimal therapy for proliferative lupus nephritis (LN) is still ongoing [1,2]. Maintenance treatment most often consists of low-dose prednisone, generally combined with either azathioprine, hydroxychloroquine or mycophenolate mofetil.

Since the prognosis of proliferative LN has improved considerably and the morbidity of therapy is substantial, the aim of treatment has changed from preventing mortality to diminishing morbidity. Because of the cumulative side effects of long-term immunosuppression, there is a constant effort to keep drug therapy at a minimum and, wherever possible, to discontinue it altogether. Compared with other manifestations of systemic lupus erythematosus however, physicians may be more reluctant to discontinue therapy in patients with LN, especially since each flare is considered a risk factor for a worse renal outcome.

So far, no randomized controlled studies have been carried out in which maintenance treatment after reaching remission was withdrawn prospectively.

Relapses during immunosuppressive therapy

Exacerbations in proliferative LN are not uncommon. Calculated renal relapse rates vary from 4 to 20 per 100 patient-years, depending on the aim of the study and duration of follow-up [3–12]. In Figure 1, we have depicted the renal relapse rate in patients with proliferative LN. To correct for the different number of patients and the duration of follow-up, we calculated the flare rate per 100 patient-years. Flare rates in three categories of patients are given: during maintenance therapy, during minimal immunosuppressive therapy (only low dose steroids and/or hydroxychloroquine), or after cessation of immunosuppression. These studies cannot be compared with each other because of differences in patient characteristics including ethnicity, definitions of remission and relapse, time period and previous and current treatment. Nevertheless, the figure gives an impression of the observed relapse rates among different groups of patients.

Clinically more meaningful is the cumulative incidence of relapses. These data also vary greatly, from 27 to 66%. The observed relapse incidence depends on several factors: (i) induction therapy: higher incidence in patients treated with steroid monotherapy compared with the treatment with a combination of prednisone and cyclophosphamide; (ii) initial treatment response: higher incidence after reaching partial remission compared with complete remission; (iii) demographic features: higher incidence in young and/or black and/or male patients; (iv) histological parameters: higher incidence with a higher activity and/or chronicity index. For a more detailed description of exacerbations of LN, we refer to a recent review by Sidiropoulos *et al*. [13].

Relapses after minimization or discontinuation of immunosuppressive therapy

Few studies have been published on the relapse frequency in patients with proliferative LN after minimization of immunosuppressive therapy or the complete discontinuation of all drugs. Stopping cyclophosphamide abruptly was associated with a rapid deterioration of renal function [14] and therefore, seems unwise.

In Table 1, we have summarized the studies in which immunosuppression was either minimized (low-dose corticosteroids and/or hydroxychloroquine) or stopped completely. Most of these studies originate in Europe, therefore these findings cannot be extrapolated to patient groups with a different ethnic background.

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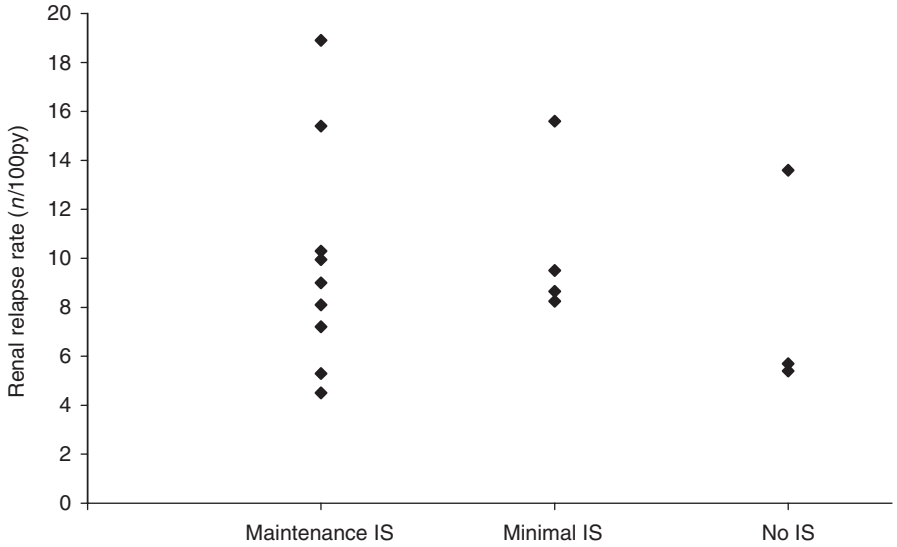

Fig. 1. Renal relapse rate (expressed in flares per 100 patient-years; *n*/100py) in patients with proliferative lupus nephritis during, after minimization or after discontinuation of immunosuppression (IS). Diamonds from top to bottom refer to the following references: during maintenance IS: [5], [7], [9], [11], [3], [10], [4], [6] and [12]; during minimal maintenance IS: [17], [18], [15] and [16]; after discontinuation of IS: [20], [19] and [22].

In 42 patients with proliferative LN who showed improvement on induction therapy (either oral cyclophosphamide with prednisone or prednisone alone) and who were followed for a mean of 43 months, Donadio *et al.* [15] observed a renal relapse rate of 8.6 per 100 patient years. Three of the 13 patients with a flare had discontinued prednisone, while the other 10 were still on maintenance therapy with low doses of prednisone.

A Spanish retrospective study described 48 patients with proliferative LN who reached remission after treatment with cyclophosphamide (orally or intravenously) and discontinued cyclophosphamide [16]. The renal relapse rate was 8.3 per 100 patient-years and the cumulative flare incidence was 56% 10 years after cyclophosphamide was stopped. However, no information was given on maintenance treatment.

A higher renal relapse rate of 15.6 per 100 patient-years was observed in 63 patients who had been treated with cyclophosphamide pulse therapy for median 31 months and had reached partial or complete remission [17]. Reaching partial remission as compared with complete remission, the time to reach remission, WHO-class IV and neurolupus at presentation were predictors of renal flare. In this cohort, maintenance therapy was left to the decision of the treating physician.

A large study by the NIH showed renal relapses in 45% of the patients who had a partial or complete response after induction therapy [18]. Patients had to be off immunosuppressive therapy, with the exception of hydroxychloroquine and low doses of prednisone. The observed flares were most often nephritic and were associated with low C4 at the time of response and African-American ethnicity.

There are only three research groups describing LN disease course after the complete withdrawal of immunosuppressive treatment. In a small group of 11 Spanish patients with proliferative LN, who had been withdrawn from both immunosuppressive drugs and corticosteroids for a minimum of 4 years, only four relapsed [19]. The calculated renal relapse rate is 5.7 per 100 patient-years.

Two Italian groups have studied patients with LN who discontinued all drugs. From 75 patients with proliferative LN, treated with methylprednisolone and pulse cyclophosphamide, 33 responded to treatment and discontinued all drugs. Eighteen renal flares occurred in 15 patients. Eighteen patients did not develop a flare and remained off treatment [20]. The same group describes that, after induction therapy but without maintenance treatment, 54% of 91 patients with proliferative LN developed a renal relapse, which was then treated with either pulse steroids and pulse cyclophosphamide or with high-dose corticosteroids alone [21].

The calculated renal relapse rate in this extended group is 15.6 per 100 patient-years. At the last follow-up (median 72 months), 43% of the relapsing patients showed a poor renal outcome (doubling of serum creatinine or end-stage renal disease).

In this issue of Nephrology Dialysis and Transplantation, Moroni *et al.* [22] report on a cohort of 102 Italian patients with proliferative LN in whom a trial was made to discontinue all immunosuppressive drugs after attaining remission. Only 44 (43%) were eligible. During reduction of immunosuppressive treatment, 12 out of 44 patients (27%) developed a flare (8 renal and 4 non-renal), while in the remaining 32 patients, immunosuppression could be stopped completely. In 17 of these, a relapse occurred (53%): 13 patients had a renal and four had a non-renal exacerbation.

Table 1. Renal relapse rate (expressed in flares per 100 patient-years; *n*/100py) in patients with proliferative LN after minimization (low dose steroids and/or hydroxychloroquine) or after discontinuation of immunosuppressive therapy

Author	No. pat	Country	Time period	FU (mean or median, months)	Definition renal relapse Screat	Uprot	Uery/sediment	Relapse rate *n*/100py
Minimized maintenance therapy								
Donadio *et al.* [15]	42	USA	1971–77	43	Renal function <75%*	>3.0* or increase >2.0*	NS	8.6
Ciruelo *et al.* [16]	48	Spain	1979–93	33 after CY discont.	NS	>0.5 or increase >1.0	>5/hpf with proteinuria or active without Uprot	8.3
Ioannidis *et al.* [17]	63	Greece	until 1999	±28 after PR or CR	>130%*	>2.0*	Active*	15.6
Illei *et al.* [18]	92	USA	1981–90	±56	**After CR**			9.5
					Proteinuric: =	Increase >2.0	Inactive	
					Nephritic:			
					mild =	Increase <2.0	>10 or casts	
					moderate =	Increase >2.0	>10 or casts	
					severe >130%	>130%	>10 or casts	
					After PR			
					Proteinuric: =	Increase >2.0	=	
					Nephritic:			
					mild <130%	Increase <2.0	Increase	
					moderate <130%	Increase >2.0	Increase	
					severe >130%	>130%	Increase	
Discontinued therapy								
Pablos *et al.* [19]	11	Spain	1971–91	77 after discont.	NS	>0.5	NS	5.7
Mosca *et al.* [20]	33	Italy	1976–98	48 after discont.	>150% **	>1.0 **	>150%**	13.6
Moroni *et al.* [22]	32	Italy	1973–2004	203 after discont.	Nephritic: >130%	Increase	Active	5.4
					Proteinuric: =	×2 or increase >2.0	NS	

No. pat = number of patients with proliferative LN; FU = follow-up; Screat = serum creatinine; Uprot = proteinuria (g/24 h); Uery = erythrocyturia; NS = not specified; discont. = discontinuation; hpf = high-power field; PR = partial remission; CR = complete remission.
*One of the criteria; **two or more criteria.

Considering the original cohort of 44 patients, complete withdrawal without disease flare could be attained in 15 patients (34%) and renal flares occurred in 21 patients (48%). At the last follow-up, 20 out of 44 patients (45%) were free of any immunosuppressive drug. Beneficial effects were shown by significantly lower cholesterol levels and a lower incidence of osteoporosis.

When and how to withdraw immunosuppressives

It is difficult, based on current available data, to precisely define the criteria that allow the identification of patients in whom immunosuppression can be stopped safely. A duration of therapy (including induction) of at least 5 years seems warranted [22]. The disease should be quiescent, both clinically and serologically. In patients who combine a number of the described risk factors for renal flares, one should be reluctant to stop therapy completely. Based on the observation that rapid tapering or abrupt cessation of immunosuppression frequently leads to serious relapses, the pace of dose reduction should be slow. During this dose reduction, frequent monitoring seems necessary, as proposed by Moroni and colleagues [22]. Besides renal parameters, this monitoring should also include serological markers of disease activity like anti-dsDNA titres and complement C3 and C4 measurements. Although their sensitivity and positive predictive value for relapses differ greatly in the literature [11,23], it is conceivable that in the absence of immunosuppression, changes in these parameters are more meaningful.

Conclusions and guidelines

Discontinuing maintenance therapy should only be attempted in those (Caucasian?) patients with proliferative LN who have been treated for at least 5 years and who have had a long period of both clinically and serologically quiescent disease, by slowly tapering the drugs and under strict and frequent surveillance. Because of the limited data available, it is difficult to predict the success rate, but discontinuation is probably feasible in about one-third of the patients. Although data are limited, a permanent decrease of renal function may occur in another one-third of the patients. These facts need to be taken into account when counselling a patient on cessation of immunosuppressive therapy.

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Conflict of interest statement. None declared.

(See related article by Moroni *et al*. NDT Advance Access published February 2, 2006. doi:10.1093/ndt/gfk073.)

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The role of combination therapy in the management of hypertension

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The relationship of blood pressure and cardiovascular risk

Data from the largest meta-analysis of hypertensive patients clearly demonstrate that increasing systolic blood pressure (BP) in any age group is associated with very significant increases in cardiovascular disease [1]. It has been shown that for every 20 mmHg increase in systolic BP, or for every 10 mmHg increase in diastolic BP, there is a doubling in the risk of cardiovascular disease. Conversely, a meta-analysis of outcome studies in the treatment of systolic hypertension demonstrated that for every 20 mmHg reduction in systolic BP there is an ~40–45% reduction in cardiovascular disease [2]. These studies have confirmed the very significant cardiovascular risk associated with hypertension and the impressive benefits that can be derived from the treatment of this disease process. Despite these findings, worldwide epidemiological data have shown that fewer than one-third of hypertensive patients achieve a BP of <140/90 mmHg [3].

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The blood pressure values achieved in clinical practice

Perhaps of even more concern is the fact that <50% of treated hypertensive patients (patients on antihypertensive medication and being followed by a physician) have a BP of <140/90 mmHg [4,5]. These are patients who have been diagnosed and treated for hypertension and for some reason inadequate BP control has been accepted. There are now several studies that clearly show that these patients remain at significant risk for cardiovascular disease. In the UKPDS study, two groups of diabetic patients were differentiated; those with 'tight' BP control and those with 'less tight' BP control [6]. Since all patients in the study were being treated with antihypertensive drugs, the comparison was really one of treated hypertensive patients with inadequate BP control compared with treated hypertensive patients with what was considered by the authors as adequate control. The difference in BP between the two groups was only 10/5 mmHg. However, patients with tight control had 44% fewer strokes and 21% fewer myocardial infarctions than those with less tight control (Figure 1). Thus, more aggressive treatment in patients already on antihypertensive treatment, but with inadequate BP control, has a significant impact on the risk of cardiovascular disease [6]. The HOT study was performed to assess whether lower BP is better: each 5 mmHg decrease in diastolic BP resulted in further decreases in cardiovascular disease—again in a group of patients in which everyone was being treated for hypertension (Figure 2) [6]. In the diabetic cohort from the HOT