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Gabriella Moroni, Mariele Gatto, Francesca Raffiotta, Valentina Binda, Eleni Frangou, Liz Lightstone, Dimitrios T. Boumpas

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Can we withdraw immunosuppressants in patients with lupus nephritis in remission? An expert debate

Gabriella Moroni[1], Mariele Gatto[2], Francesca Raffiotta[1], Valentina Binda[1], Eleni Frangou[3], Liz Lightstone[4], Dimitrios T Boumpas[5]

[1] Unita' Operativa di Nefrologia e Dialisi Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano. Italy

[2] Unit of Rheumatology, Department of Medicine, University of Padova, Italy

[3]Nicosia General Hospital, Nicosia Cyprus; and Medical School, University of Cyprus, Nicosia, Cyprus

[4] Imperial College Lupus Centre, Section of Renal Medicine and Vascular Inflammation, Department of Medicine, Faculty of Medicine, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, UK

[5]Joint Rheumatology Program, 4th Department of Medicine, "Attikon" University Hospital, National and Kapodistrian University of Athens Medical School and Biomedical Research Foundation of the Athens Academy Athens, Greece; and Medical School, University of Cyprus, Nicosia, Cyprus

Corresponding Author

Dimitrios T Boumpas, "Attikon" University Hospital 1 Rimini str, Haidari 12462, Athens Greece

Email boumpasd@uoc.gr, boumpasd@med.uoa.gr

Abstract

Lupus nephritis (LN) treatment requires an initial intensive period of therapy followed by a long-term maintenance treatment in order to stabilize disease control and eventually reach renal remission. In this section, Authors discuss the feasibility of safely lowering and even suspending maintenance therapy in LN patients having entered remission, highlighting hurdles in predicting the depth and durability of disease quiescence together with the need for minimizing potentially toxic therapies. Even though no firm conclusions can still be drawn, the treating physician has to find the wise balance between disease control and treatment-related drawbacks by following patients closely and recognizing as early as possible the ones who are likely to reach a deep and durable renal remission; there is consensus that is these are the only patients in whom a potential safe complete withdrawal can be foreseen so far.

Keywords: lupus nephritis, immunosuppression, organ damage, remission

1. Introduction

Lupus nephritis (LN) is a major predictor of poor prognosis in patients with systemic lupus erythematosus (SLE), also contributing to disability and direct and indirect health care costs [1]. Indeed, despite improvements in diagnosis and treatment, the standardized mortality ratio in SLE patients is about 3 times higher than that of the general population, with renal disease being one of the most common causes of death [2-4] and the most important predictor of mortality within the SLICC/ACR Damage Index [5]. End-stage renal disease (ESRD) develops in up to one third of LN patients and has a high socioeconomic impact since the great majority of these patients are younger than 50 years old [6,7]. In the United States in 2009, SLE patients with ESRD had the highest annual mean cost of treatment, ranging from $43,000-$107,000 per patient per year [7].

Treatment of LN consists of an initial period, usually months, of intensive immunosuppression (named "induction therapy") to control immunologic activity, minimize tissue injury and induce disease remission. This phase is followed by a "maintenance therapy" that corresponds to a longer period of less intensive and less toxic treatment to retain remission and prevent subsequent flares, yet still at the cost of prolonged exposition of patients to long-standing immunosuppression which is endowed with a number of side effects [8]. In fact, while there is general agreement that following a timely biopsy, LN requires early aggressive therapy to achieve remission, the type of induction or maintenance therapy and the duration of immunosuppression after achieving response or remission remain a matter of controversy [9,10].

In this article, Prof. Gabriella Moroni and Prof. Dimitrios Boumpas debate on how to manage long-term treatment and particularly on how and when to stop immunosuppressive maintenance therapy in LN patients reaching remission. The actual debate was held during the CORA meeting held in Bologna, Italy, on March 9-11, 2017.

2. Can we withdraw immunosuppressants in patients with lupus nephritis in remission?

Yes, we can! (Prof. Gabriella Moroni)

There is agreement that early diagnosis and aggressive treatments of LN exacerbations are of paramount importance to achieve renal remission and prevent the development of irreversible renal dysfunction [11,12]. Throughout the last decades, better supportive care and an immunosuppressive approach tailored on the grounds of the clinical and histological characteristics at presentation have resulted in a progressive improvement of patient and renal survival [13,14]. In our cohort of patients with a biopsy proven LN performed before December 1990, the patient survival was 97% at 10 years and 91% at 20 years and the renal survival was 93% at 10 years and 87% at 20 years [15]. Due to the improved survival, however, SLE patients have a lifelong burden of both the disease as well as continuous steroids and immunosuppressive therapy. Based on randomized controlled trials, the EULAR/EDTA recommends to continue immunosuppression for at least 3 years, but no suggestion is given on what to do after 3 years [16]. On the other hand, there are no demonstrations that, in SLE patients in remission, the ongoing, long-term administration of glucocorticoids and immunosuppressive therapy has any clinical or serological benefit. Instead, it is well known that the prolonged therapies, presumed necessary to maintain the remission of the disease, cause in the short and long-term a significant increase of mortality and morbidity. Thus, the issue of a possible withdrawal of therapy in patients who achieved stable remission urgently emerged.

2.1 Side effects of glucocorticoids and of immunosuppressive drugs in the short and long-term

Treatment of LN normally comprises glucocorticoids with either cyclophosphamide (CYC), mycophenolate mofetil (MMF), azathioprine (AZA), and/or calcineurin inhibitors. Unfortunately, all these drugs have a low therapeutic index and may be responsible for morbidity and even life-threatening side effects in the short and long-term **(Table 1 and 2).** It is well known that toxicity of corticosteroids and immunosuppressive agents is related not only to the dose but also duration of treatment**.** Even small doses of corticosteroids, if continued in the long-term, can lead to significant

morbidity [17]. An increasing number of studies reported the independent predictive value of corticosteroids on damage accrual in SLE. Petri et al. [8] evaluated the predictors of damage accrual in the large Hopkins Lupus Cohort. At multivariate analysis, the strongest predictors of damage accrual were age and current corticosteroid dose. The predictive value of corticosteroids for damage accrual persisted even after adjusting for levels of SLE disease activity. Similar results were reported by the SLICC inception Cohort. Levels of disease activity, use of corticosteroids and hypertension all significantly influenced damage accrual in SLE patients [18].

Premature atherosclerosis has emerged as a major cause of late morbidity and mortality in SLE patients. The incidence of myocardial infarction and stroke were estimated to be 8.5, and 10 times more frequent in SLE women than in the general population [19,20]. Significant positive associations have been reported between glucocorticoids and traditional cardiovascular risks factors such as total cholesterol and triglycerides levels and arterial hypertension [21]. The increase in cardiovascular disease in SLE is not fully explained only by traditional cardiovascular risks factor; rather disease activity is a significant contributor to the risk [22]. However, glucocorticoids have been found to be independently associated with the increased risk of cardiovascular disease in multivariate analysis after controlling for disease activity [23].

CYC too, through the development of premature ovarian failure, may contribute to the premature development of cardiovascular diseases in SLE women **(Figure 1).** In the long term, an increased risk of malignancy is the most serious complication that can occur with immusuppressive drugs. The oncogenic risk of immunosuppressors depends on intensity and length of treatment. The risk of malignancy increases when oral CYC is administered for more than 6 months, and the cumulative dose exceed 360 mg/kg. [24]. Regarding AZA, a systematic review in multiple sclerosis hypothesized that a long-term risk of cancer may be related to a treatment duration above 10 years and cumulative dose above 600 grams [25].

Hence, a period free from corticosteroids and immunosuppressive agents could be useful to prevent iatrogenic morbidities.

2.2 Available data on withdraw of therapy in SLE and in LN

2.2.1 Available data on SLE

Whether a complete withdraw of therapy is possible in SLE while minimizing the risks of a reactivation of the disease remains an unanswered question. A recent survey assessed the treatment attitude of clinicians who follow LN patients. Twenty-nine percent of the participants reported they continue corticosteroids in any conditions, 38% attempt to discontinue corticosteroids only in some conditions and 33% attempt to discontinue corticosteroids after the achievement of remission [26]. In spite of these declarations, few data are available about withdrawal of therapy in SLE. The largest experience on withdrawal of therapy was reported by Drenkard et al. [27]. In a cohort of 667 SLE patients, 156 (23%) were able to stop therapy and maintain the remission for a mean of 5.8 years. Of them, 82 patients (52%) continued without therapy until the last observation, the other 75 patients had new flares, restarted therapy and the majority of them entered remission again. Recently, the possibility of complete withdrawal of therapy in SLE gained more attention. In the GLADEL cohort, 20.2% of SLE patients were able to completely withdraw therapy for 1 year, and 9.7% for 3 years [28]. Steiman et al. reported 2.4% SLE patients taking no medications for ≥5years [29], while Zen et al. reported the complete withdrawal of therapy in 7.1% of SLE patients for ≥ 5 years [30].

2.2.2 Available data on LN

Few data are available in patients with LN. Pablos et al. discontinued CYC in 11 patients with class IV LN who reached complete remission. Four patients relapsed following therapy withdrawal (36%). Clinical remission could not be achieved with re-induction therapy in two patients [31]. Mosca et al. discontinued CYC in 33 patients with diffuse proliferative LN previously treated with pulse steroids and a short course of pulse CYC. Fifteen patients (45%) experienced a renal flare after the discontinuation. Out 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 [32]. Euler et al. [33] reported on 14 patients with severe SLE treated with a

protocol of plasmapheresis and high-dose pulse CYC 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. In a small randomized trial, 15 patients with class III or IV LN in complete or partial remission, were randomized to continue prednisone 7.5 mg/day (8 patients) or substitute prednisone with placebo (7 patients). Immunosuppressive drugs were continued in all patients. Over 36 months, severe flares occurred in four (50%) patients in prednisone therapy compared to one patient (14%) in the placebo group. Based on the good results of the study the authors concluded that a large trial of prednisone maintenance therapy compared to withdrawal is feasible [34].

2.3 Safe withdraw of immunosuppressants in SLE

2.3.1 How and when to withdraw immunosuppressants in SLE

The above reported data suggest that therapy may be withdrawn for a given time span at least in some patients. The essential prerequisite for a safe withdraw of therapy is patient remission. The achievement of remission is an important target, as it has been demonstrated that renal and patient long term survival are significantly better in patients who achieve remission [35,36]. Prolonged remission was associated with a reduced damage accrual than in unremitted patients [30,37]. During discontinuation of therapy, the most delicate phase is the reduction of treatment. We have learned from old studies that an abrupt discontinuation of treatment may lead to severe and even irreversible renal failure [38]. For this reason the medications tapering should be slow, progressive and under strict medical surveillance. Renal and extra-renal SLE flares are the potential risks of therapy withdrawal; however the available data do not demonstrate increased risk of flares after therapy withdrawal in comparison to maintenance therapy and minimal immunosuppressive therapy [39].

2.3.2 Our approach to withdraw of immunosuppressants in LN

Since the 80s we focused on this problem and published our first results about therapy withdrawal in LN in a small group of patients [40]. Based on the good results we continued this approach and published in 2006 and 2013 our experience in a larger number of patients [41,42]. We were able to completely stop treatment in 52 of 161 (32%) patients with class III, IV or V LN. The decision of interrupting therapy was taken for those patients who had achieved a stable clinical remission, and did not show any renal or extra-renal flare during a slow, progressive reduction of corticosteroids and immunosuppressive drugs. The maneuver was made under strict medical surveillance. Out of 52 patients, 32 (61.5%) never developed new flares and continued without any therapy for the subsequent 101.8 months of observation (range 44-180 months) after withdrawal of therapy. The other 20 patients (38%) developed new flares after a median of 37 months (range 20-77 months) after stopping therapy; 10 patients developed proteinuric flares, 5 nephritic flares and 5 extra-renal flares. All patients restarted therapy and entered remission again. Fourteen out of the 20 patients could again stop treatment after resolution of flare. At the end of a median follow-up of 286 months after first withdrawal of therapy (range 183-312 months) half of patients who experienced new flares were still off treatment. These patients spent around 40% of their cumulative follow-up without corticosteroids or other immunosuppressive drugs.

We tried to identify which factors may predict the complete and persistent withdrawal of therapy. Significantly more patients who never had new flares after withdrawal of therapy, received cytotoxic therapy in addition to steroids as maintenance after the induction treatment (62.5% vs 25% respectively p=0.019). This could have contributed to better control the activity of the disease. As a matter of fact, the importance of maintenance immunosuppressive therapy after induction in consolidating the remission is well known [43]. The median duration of treatment before interruption was longer in patients who never flared than in those who developed new flares, being respectively 98 months and 31 months (p= 0.01). The duration of remission before withdraw of therapy also seems 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 (52.8 vs

12.0 months, respectively p=0.000). In comparison with patients who had new flares, a significantly higher number of those without flares were on hydroxychloroquine treatment before and after withdraw of therapy (52% vs10%, p=0.004). This antimalarial agent is part of the immunomodulatory regimen used to treat patients with SLE and may contribute to prevent exacerbations of lupus [44,45].

At any rate, 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 developed new flares after interruption of treatment. Only two patients in the group with new flares showed a doubling of serum creatinine around 20 years after the diagnosis of LN. No patient in either group entered end stage renal disease **(Table 3**).

The benefits of stopping treatment are clearly demonstrated by comparing the 109 patients of our cohort who continued immunosuppressive therapy without interruption with the 52 who stopped therapy **(Table 4).** At the last observation, fewer patients who stopped therapy doubled their serum creatinine and none of them developed end stage renal disease. The incidence of proteinuric flares and nephritic flares were all significantly lower in the group without treatment (0.04 proteinuric flares /patient/year vs 0.07; 0.01 nephritic /patient/year vs. 0.05 respectively). Obviously, patients who continued therapy had a more aggressive disease and this may account for these differences. Nevertheless, the median levels of serum cholesterol and, even more importantly, incidence of arterial hypertension and of cardiovascular events were significantly less frequent in patients who stopped therapy in spite of a longer median follow-up of this group (19 years vs. 11).

In summary, we were able to completely withdraw therapy in around 1/3 of our patients; 60% of them never had to start therapy again. In these patients withdrawal of therapy resulted in improvement of patients' quality of life and in reduction of damage accrual.

Based on our own experience, discontinuation of therapy should be done only in selected cases, i.e. patients who received maintenance therapy for at least 5 years and are in complete renal remission for at least 3 years. The tapering of therapy before complete withdrawal may require many months

and must be done under strict medical surveillance. Antimalarial agents are helpful in maintaining the remission after withdrawal of therapy. A multicentre randomized controlled trial is necessary to confirm our results.

3. **Can we withdraw immunosuppressants in patients with LN in remission? No, we can't (Prof. Dimitrios T Boumpas)**

3.1 Remission is associated with a favorable outcome in LN but is both delayed and occurring in less than half of them

A previous study involving 86 severe LN patients treated with aggressive initial therapy showed remission in 37 patients (43%) after 10 years of follow-up [46]. Patient survival rates were 95% in patients that achieved remission and 60% in patients that did not. Renal survival rates were 94% at 10 years in the remission group whereas 31% in the non-remission group. Failure to attain remission was predictive of ESRD, suggesting that in patients with severe LN, a renal remission is associated with dramatic improvement in the long-term patient and renal survival [46]. In a study of 86 patients with diffuse LN [47], patients with complete remission had a lower serum creatinine and chronicity index when compared to patients with partial or no remission. Even a partial remission in LN was associated with a significantly better patient and renal survival compared with no remission. Collectively, disease remission and mainly early remission [48] can predict a better outcome in SLE, whereas active SLE patients exhibit a poor long-term prognosis. Renal survival is increased in patients with complete or partial remission when compared to patients with severe disease, and overall survival at 20 years is significantly increased in patients with complete remission [49].

In SLE, the goal is remission of systemic symptoms and organ manifestations, while in LN the goal is the long-term preservation of renal function and the avoidance of ESRD. We have shown that complete renal response, usually defined as stable or improved renal function with low grade proteinuria (<0.5-1 g/day) plus or minus inactive urine sediment after immunosuppression, is

associated with significantly lower risk (LR 0.14) for progression to ESRD [50]. Definitions of renal remission in the short-term (6-24 months) based on proteinuria, serum creatinine and urine sediment have been used, but consensus on the levels of these has not been achieved. Importantly, there are no studies providing evidence that these definitions may predict a favorable long-term renal outcome. Despite vigorous research, there is currently no agreement on how to define remission in SLE. Recently, an international task force was convened to achieve consensus on potential definitions for remission in SLE. They provided a framework where remission was distinct from cure and could be identified as a desirable outcome with at least the absence of major symptoms and signs of SLE. Remission was approached at a global level; however, it could also be defined at an organ level. Since complete renal remission is associated with a favorable outcome, they suggested that sustained remission could be a state associated with a low possibility of adverse outcomes. There was agreement on not distinguishing serologically active from inactive patients due to the high risk of relapse in the former, and that patients on moderate- or high-dose glucocorticoids could not be considered as patients in remission. Importantly, the task force did not specify the length of time that a remission had to be sustained in order to qualify, mainly due to concerns about the relapsing-remitting nature of the disease. It also provided a framework that distinguished "remission off therapy" from "remission on therapy". This definition of remission has been used by Fischer et al. who showed that in 1555 patients sustained remission for more than 5 years was achieved in just 1.2%, 2.0%, 0.6% and 0.7% of patients that met the criteria for clinical remission, complete remission, clinical remission on treatment and complete remission on treatment respectively. To investigate the safety of immunosuppression withdrawal in patients with LN in remission, generally accepted definitions of remission and its duration must be applied [51].

3.2 Renal flares accumulate renal damage and increase the risk of death

LN can relapse after an initial remission even beyond 10 years of remission [52]. Each renal flare is associated with new damage to the kidneys that contribute to loss of nephrons, fibrosis and deterioration of renal function [53]. The relapse rate after immunosuppression for diffuse

proliferative LN is 10-66% depending on the initial severity of the renal disease, the treatment regimen used, the ethnicity of the patients, the definitions of relapse, and the duration of observation [43]. We analyzed 92 patients with proliferative LN who initially responded to immunosuppression and found that renal flares occurred in 45% of patients over a mean observation period of 117 months when immunosuppression was stopped [50].

Renal relapse in LN has been shown to have adverse prognostic significance with most patients progressing to doubling of serum creatinine. Hill GS et al. showed that 18/71 patients (25%) who progressed to doubling of serum creatinine either failed to respond to therapy (7/18, 38%) or relapsed after initial response (11/18, 61%). Of the initial responders, 11/56 (19%) experienced subsequent renal flares, with renal relapse being a major risk factor for progression to doubling serum creatinine. Nephritic relapses were more frequent and had a worse prognosis than proteinuric relapses [54]. Renal relapse was associated with a high rate of progression to doubling serum creatinine and ESRD, since despite adequate treatment, exacerbations of renal disease, especially nephritic flares, could result in irreversible glomerular damage leading to global or focal glomerulosclerosis [55]. The flare-associated risk of CKD or ESRD is mainly due to nephritic flares, that are characterized by an increase in serum creatinine and hematuria. Proteinuric flares, that are characterized by proteinuria and not an increase in serum creatinine, confer less long-term risk to renal damage [36,43,55]. After initial response, renal disease exacerbations, mainly severe nephritic flares, have an increased risk (HR 13,9; LR 11,8] of developing irreversible renal damage or death. Accrual organ damage is a strong prognostic factor for subsequent damage accrual and death, irrespective of whether the damage occurred early or late [51]. Also, severe flares necessitate the use of moderate to high doses of glucocorticoids and re-introduction or intensification of immunosuppression in 17-38% of patients [56,57]. Whereas the EULAR/ERA-EDTA recommendations divided flares into nephritic and proteinuric, the ACR and KDIGO guidelines did not, suggesting that renal flares could be considered as individual acute kidney injury (AKI) events that add to preexisting tissue damage [58]. Based on these, the Ohio SLE study showed a significant

association between any renal flare and new onset CKD, and a trend between renal flare and progressive CKD in patients with proliferative or membranous LN followed for at least 3 years. The number of new renal flares per year and the time spent in renal flare were significantly higher in patients who had poor long-term renal outcomes. Patients who spent more than 30% of time in renal flare had a 20-fold higher risk of developing new or progressive CKD [59]. Two studies, one in 91 Caucasian SLE patients with proliferative LN and the other in 135 Egyptian patients showed that both nephritic and proteinuric flares were associated with an adverse outcome [60,61].

Collectively, these data show that LN can relapse even 10 years after remission. Each renal flare has adverse prognostic significance and associates with new damage on the kidney. According to their number and severity, flares increase renal damage. Accumulation of irreversible organ damage predicts further damage, additional morbidity and early mortality. Together, these data suggest that in the absence of reliable predictors of flares, the primary goal in SLE should be the prevention of flares rather than withdrawal of immunosuppression since maintenance immunosuppressive therapy decreases the risk of flare.

3.3 Are there enough data to support that withdrawal of immunosuppression reduces side-effects? The case for minimization of corticosteroids

Immunosuppression is associated with medical costs and short- and long-term adverse effects, including infections, cardiovascular disease and malignancies. In a study of 2054 SLE patients (92% female, 56% Caucasian, 37% African-American, mean age at diagnosis 33 years), the SLICC/ACR Damage Index was calculated retrospectively. During follow-up, the risk of damage was higher for those who were on glucocorticoids, and after adjustment of other variables glucocorticoids emerged as one of the most important predictors of damage accrual, pointing towards the need for control of disease activity without corticosteroid reliance (8). In a retrospective study of 310 patients in Canada, higher past-year corticosteroid dose and higher past-year disease activity were independently associated with significantly higher overall 2-year coronary heart disease risk [23]. The EULAR-ERA EDTA recommendations suggest gradual withdrawal of

glucocorticoids to be attempted in patients improving after initial treatment and remaining in remission for at least 3 years after subsequent immunosuppression. However, when clinical remission was defined as absence of signs, symptoms, urinary and hematological abnormalities in steroid-free patients, fewer than 2% of patients remained in complete remission longer than 5 years [62]. Also, 60% of serologically active but clinically quiescent patients who did not receive treatment to accumulate less organ damage over a 10-year period, experienced a flare after a median of 3 years. When steroids were re-introduced, steroid-related damage was increased [63]. When corticosteroids cannot be tapered off, a dose lower than 6 mg prednisone does not appear to cause damage in SLE. Such low doses were not associated with increased mortality in SLE patients with minimal disease activity [64].

CYC use has adverse effects such as bone marrow, gonadal, and bladder toxicity, as well as malignancy. For these reasons, CYC is not recommended as a maintenance therapy in LN, therefore it is "withdrawn" after the induction phase to be substituted by either MMF or AZA. MMF is effective as both an induction and a maintenance therapy in LN, and its major side-effects are gastrointestinal symptoms, bone marrow toxicity that occurs mainly in hypoalbuminemic patients, and dose-dependent increased risk of infections. Both the EULAR/ERA-EDTA and the ACR recommend azathioprine can be used as an alternative to MMF for maintenance immunosuppressive therapy in proliferative LN. AZA is effective and cheap, it reduces the risk of renal flare and can be used as a steroid-sparing agent. Apart from frequent gastrointestinal symptoms, other adverse effects are rare, dose-dependent and idiosyncratic. Together these data suggest that a strategy that minimizes the use of corticosteroids with AZA or lower doses of MMF has a low risk of side effects.

3.4 Is it safe to withdraw immunosuppression in LN? Results from available data

Only few studies are available on withdrawal of immunosuppression in SLE. To characterize the clinical course of SLE patients with prolonged remission (for more than 5 years), Steiman AJ et al.*[29]*, analyzed 1613 SLE patients and found that only 38/1613 (2.4%) patients achieved

prolonged remission while taking only antimalarials and not corticosteroids or immunosuppressants (mean duration was 11.5 ± 6.4 years). Of these, 27 patients (71.0%) had relapsing-remitting disease and 11 (28.9%) had monophasic disease. Importantly, only 34/1613 patients (2.1%) achieved prolonged remission while taking steroids and/or immunosuppressants, with mean duration 8.5 ± 2.9 years; and 12 of them (35.3%) experienced flare [29]). Zen M et al. [30] reported that, during a 5-year follow-up, 140/223 (62.5%) of Caucasian patients with SLE did not achieve prolonged remission. Only 16 patients (7.1%) achieved prolonged remission on antimalarials only, 33 (14.7%) on immunosuppressants and antimalarials but off corticosteroids, and 35 (15.6%) on low-dose steroids plus antimalarials and immunosuppressants. 1/16 (6%) of remitted patients had renal disease, and glomerulonephritis was independently associated with the absence of prolonged or clinical remission [30].

Again, when clinical remission was defined as absence of signs, symptoms, urinary and hematological abnormalities in steroid-free patients, fewer than 2% of patients remained in complete remission longer than 5 years [62]. Moreover, 60% of serologically active but clinically quiescent patients that did not receive treatment to accumulate less organ damage over a 10-year period, experienced a flare after a median of 3 years. When steroids were re-introduced, steroid-related damage was increased [63]. To investigate whether low-dose prednisone prevents relapses, Galbraith et al. [34] allocated 15 patients with a history of class III or IV LN who achieved at least partial remission and remained on prednisone, to either prednisone continuation (n=8) or prednisone withdrawal (n=7). Over 36 months, 4/8 (50%) on prednisone continuation exhibited flares whereas only 1/7 (14%) experienced flare on the prednisone withdrawal group. This pilot randomized controlled trial was small and not designed to assess the efficacy or safety of maintenance with low-dose prednisone.

To investigate the safety of corticosteroid and immunosuppression withdrawal in patients with proliferative LN, therapy was gradually withdrawn in 73 patients who were in remission. 21/73 (28.7%) of patients experienced lupus flares during reduction of therapy, so therapy was re-

instituted. 32/52 (71.2%) patients remained with no therapy for a median of 101.8 months. However, the increased percentage of 38.4% (20/52) patients had at least one flare in a median of 37 months after therapy withdrawal. Of them 10% (2/20) died and 10% (2/20) developed renal insufficiency at the last observation [41,42,65].

Recently, to determine the clinicians' approaches to management of SLE patients in clinical remission, Ngamjanyaporn P et al. [66] undertook an internet-based study of 130 clinicians from 30 countries and found that preferences in withdrawing or reducing treatment vary considerably. It was found that, even after 5 years of clinical remission in patients with a history of major organ involvement, 40% of physicians preferred to continue steroids and 80% preferred immunosuppression to be unchanged if any evidence of active serology [66]. In addition to the unwillingness of physicians to withdraw immunosuppression in SLE, only few studies are available on withdrawal of immunosuppression in LN in remission.

In fact, even the proponents of withdrawal of immunosuppression admit the challenges of withdrawing therapy by stating that *"discontinuation of therapy should be applied only in selected cases, i.e. patients who received maintenance therapy for at least 5 years and are in complete renal remission for at least 3 years… and that drugs should be tapered off very slowly and under strict surveillance (65).* In our experience, withdrawal is applicable for up to 5% -10% of patients. For the majority of the remaining cases, we are reluctant to discontinue immunosuppressive therapy. LN can relapse after an initial remission even beyond 10 years of remission. Deep remissions are rare in LN (especially after induction with MMF), flares are not uncommon (observed in approximately 1 out of 3 patients) especially within the first 5 years of therapy, severe flares are less likely to respond to reintroduction of therapy and have a substantial risk for irreversible renal damage. Discontinuation of therapy increases the risk of flare. Flares are not uniform and are hard to predict; to carry a meaningful discussion about discontinuing immunosuppressive therapy we need sensitive and reliable predictors of renal flares which we lack at present. On the other hand, prediction of ESRD is much easier. Patients at high risk for developing ESRD (with a likelihood ratio ranging

from 5 to 24) include those with CKD and GFR less than 60 ml/ min, patients with history of renal flare or incomplete renal response and residual proteinuria of more than 0.7 g/day, and anemic patients with hematocrit of less than 33%. In such patients, discussions about discontinuation of immunosuppressive therapy are misdirected and do not serve the needs of the patients. The availability of less toxic maintenance therapy such as AZA, hydroxychloroquine and the emerging data suggesting that biologic therapies, such as belimumab, may be useful in preventing renal flares [67,68] have certainly made maintenance therapy more acceptable. While continuing to search for more effective therapies to achieve deeper remissions and more reliable and sensitive molecular and biologic markers for this, the community needs to direct its efforts more to minimizing the use of cortisteroids and the prevention of the increased cardiovascular morbidity, stroke and serious infections rather than withdrawal of therapy.

4. Concluding remarks

The issue of immunosuppressant therapy tapering in LN patients still remains controversial, with data varying concerning the rate of new flares after withdrawal of maintenance therapy. Although the percentage of LN patients reaching a deep and prolonged remission is still lower than hoped, those patients who do might be candidates to undergo cautious immunosuppression tapering under tight control. In contrast, patients displaying an active, possibly relapsing-remitting disease eventually culminating in renal insufficiency will be discouraged from ever interrupting their maintanance treatment. Between the two extremes lays a sizeable gray zone of patients with a fluctuating disease course, incapable of reaching a long-term remission and displaying a suboptimal LN control with residual signs of activity despite mid-to-high background steroids. An unambiguous definition of durable renal remission is urgently needed as well as a wider panel of reliable biomarkers useful in predicting disease course in the mid- and long-term.

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Bullet points

- Deep remissions are rare in LN, and flares occur in almost 50% within the first 5 years of therapy; sensitive and reliable predictors of renal flares are not available.
- Emerging data suggesting that biologic therapies such as belimumab may be useful in preventing renal flares and can make maintenance therapy more acceptable.
- We need to strive for more effective therapies to achieve deeper renal remissions and more reliable and sensitive molecular and biologic markers of remission.
- Minimizing the use of corticosteroids and preventing cardiovascular morbidity, stroke and serious infections, should be the primary concern and not withdrawal of therapy.

Table 1. Main side effects of glucocorticoids

Arterial hypertension	Inhibition of pituitary-adrenal axis
Diabetes mellitus	Osteoporosis
Obesity and Cushingoid appearance	Acne, Bateman's purpura
Infection	Myopathy
Hyperlipidemia	Pseudotumor cerebri
Psychiatric reaction	Cataract, glaucoma
Gastrointestinal complications	Growth restriction in children

Table 2 Main side effects of immunosuppressive therapy in use in lupus nephritis.

	Cyclophosphamide	Azathioprine	Mycophenolate Mofetil	Calcineurin inhibitors
Infections	++	+	++	+
Bone marrow inhibition	++	++	+	-
Bladder toxicity	++	-	-	-
Gonadal toxicity	++	-	-	-
Teratogenecity	+++	-	+++	-
Liver toxicity	+	+	-	-
Malignancy	++	++	**?**	+
Gastrointestinal toxicity	+	-	+++	+
Nephrotoxicity	-	-	-	+
Arterial hypertension	-	-	-	+
Hypertrichosis	-	-	-	+
Glucose intolerance	-	-	-	+
Hyperlipidemia	-	-	-	+
Neurological complications	-	-	-	+

Table 3: Clinical status at last follow-up of lupus nephritis patients who did not have new flares and of those who had new flares after complete withdrawal of therapy

	No new flares 32pts	New flares 20pts	p
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
Chronic renal insufficiency	0	2 (10%)	NS
Dialysis	0	0	
Deaths	2 (6.2%)	2 (10%)	NS

Values are expressed as median and interquartile ranges

Table 4 Clinical status at last observation of 52 lupus nephritis patients who withdraw and of those who never withdraw therapy

	Withdraw therapy 52 pts Follow-up 269 months	No withdraw therapy 109 pts Follow-up 190 months	P 0.00
Deaths N° pts	4 (7.6%)	11(10.1%)	ns
Chronic renal insufficiency Number of patients	2(3.8%)	31 (28.4%)	0.000
Hemodialysis 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

Values are expressed as median and interquartile ranges

**- Withdraw therapy patients: Myocardial infarct 3 patients, Cerebral thrombosis 3 patients

- No withdraw therapy : Myocardial infarct 8 patients, Cerebral thrombosis 15 patients, pheripherical arterial thrombosis 2 patients, transient ischemic attack 5 patients

Figure 1: Contributors to development of premature atherosclerosis in SLE