When and How Is It Possible to Stop Therapy in Patients with Lupus Nephritis
A Narrative Review

Gabriella Moroni,1 Giulia Frontini,1 and Claudio Ponticelli2,a

Abstract
Glucocorticoids and other immunosuppressants still represent the cornerstone drugs for the management of SLE and lupus nephritis. The refined use of these drugs over the years has allowed us to obtain stable disease remission and improvement of long-term kidney and patient survival. Nevertheless, a prolonged use of immunosuppressive agents may be accompanied by severe and even life-threatening side effects. Theoretically, a transient or even definitive withdrawal of immunosuppression could be useful to prevent iatrogenic morbidities. For many years, however, the risk of SLE reactivation has held clinicians back from trying to interrupt therapy. In this review, we report the results of the attempts to interrupt glucocorticoids and other immunosuppressive agents in lupus nephritis and in SLE. The available data suggest that therapy withdrawal is feasible at least in patients enjoying a complete clinical remission after a prolonged therapy. A slow and gradual reduction of treatment under medical surveillance is needed to prevent flares of activity. After therapy withdrawal, around one-quarter of patients may have kidney or systemic flares. However, most flares may respond to therapy if rapidly diagnosed. The other patients can enter stable remission for even 20 years or more. The use of antimalarials can help in maintaining the remission after the withdrawal of the immunosuppressive therapy. A repeated kidney biopsy could be of help in deciding to stop therapy, but given the few available data, it cannot be considered essential.

Introduction
The last European League Against Rheumatism-European Dialysis and Transplant Association-European Renal Association (EULAR-EDTA-ERA) guidelines recommended to initiate therapy with mycophenolate or low-dose intravenous cyclophosphamide, both combined with intravenous methylprednisolone pulses followed by low-dose oral prednisone. A combination of mycophenolate with a calcineurin inhibitor or high-dose cyclophosphamide is an alternative for patients with nephrotic-range proteinuria and adverse prognostic factors. Hydroxychloroquine is recommended with regular ophthalmologic monitoring for class 3 or 4 lupus nephritis and in SLE. The available data suggest that therapy withdrawal is feasible at least in patients enjoying a complete clinical remission after a prolonged therapy. A slow and gradual reduction of treatment under medical surveillance is needed to prevent flares of activity. After therapy withdrawal, around one-quarter of patients may have kidney or systemic flares. However, most flares may respond to therapy if rapidly diagnosed. The other patients can enter stable remission for even 20 years or more. The use of antimalarials can help in maintaining the remission after the withdrawal of the immunosuppressive therapy. A repeated kidney biopsy could be of help in deciding to stop therapy, but given the few available data, it cannot be considered essential.

Results in Lupus Nephritis
Until recently, discontinuation of immunosuppression in lupus nephritis was considered impractical for the fear that it could trigger flares and irreversible kidney damage (Table 1). This concern was confirmed by the rapid increase of disease activity and serum creatinine when treatment was abruptly discontinued (6). However, a few years later, other reports showed that withdrawal of immunosuppressive therapy was successful if drugs were discontinued with a slow and progressive tapering under strict medical surveillance (7–9). The largest trial of immunosuppressive therapy interruption in lupus nephritis was reported by Moroni et al. (10), who gradually withdrew treatment in 73 of 161 patients (45%). Before reduction of immunosuppressive drugs, all of the patients were in stable clinical

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1909
## Table 1. Rate of recurrence of SLE flare after withdrawal of therapy in patients with SLE and in patients with lupus nephritis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of Study</th>
<th>No. of Patients with SLE (% of Patients with Lupus Nephritis)</th>
<th>Criteria for Withdraw Therapy</th>
<th>Drug Withdrawn for Study</th>
<th>No. (%) of Patients Who Stopped the Study Drug</th>
<th>No. (%) of Patients Taking No Other Immunosuppressant after Stopping the Study Drug</th>
<th>Follow-Up after Stop Therapy, mo/yr</th>
<th>No. of Patients (% Who Had Flares)</th>
<th>Flare Rate, no./yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lupus nephritis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barber et al. (9) 2006</td>
<td>R</td>
<td>16 (100)</td>
<td>≥3 years therapy + complete remission</td>
<td>Steroids + IS</td>
<td>16 (100)</td>
<td>16 (100)</td>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moroni et al. (10) 2013</td>
<td>R</td>
<td>198 (100)</td>
<td>Clinical remission ≥12 months</td>
<td>Steroids + IS</td>
<td>73 (36.9) attempted, 52 (26.3) succeeded 7 (46.7)</td>
<td>52 (100)</td>
<td>288</td>
<td>20 (38.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Galbraith et al. (15) 2014</td>
<td>Pilot</td>
<td>15 (100)</td>
<td>Class 3 or 4 lupus nephritis</td>
<td>Steroids</td>
<td>NA</td>
<td>NA</td>
<td>116.5</td>
<td>1 (14) without steroid 19 (22.8)</td>
<td>1.96</td>
</tr>
<tr>
<td>Zen et al. (11) 2021</td>
<td>R</td>
<td>238 (100)</td>
<td>Stable remission</td>
<td>IS</td>
<td>83 (34.8)</td>
<td>NA</td>
<td>11.6</td>
<td>19 (22.8)</td>
<td>1.96</td>
</tr>
<tr>
<td>Mathian et al. (16) 2020</td>
<td>RCT</td>
<td>124 (37.9)</td>
<td>Clinical remission ≥12 months</td>
<td>Steroids</td>
<td>63 (50.8)</td>
<td>47 (75)</td>
<td>12</td>
<td>17 (27)</td>
<td>17</td>
</tr>
<tr>
<td>Goswami et al. (13) 2019</td>
<td>R</td>
<td>148 (52.7)</td>
<td>Remission = SLEDAI-2K=0</td>
<td>Steroids</td>
<td>148 (100)</td>
<td>64 (43.2)</td>
<td>17.9</td>
<td>31 (20.9)</td>
<td>20.8</td>
</tr>
<tr>
<td>Tani et al. (12) 2019</td>
<td>R</td>
<td>148 (53.3)</td>
<td>Complete or clinical remission</td>
<td>Steroids</td>
<td>91 (61.5) attempted, 77 (52) succeeded 139 (43.5)</td>
<td>41 (53)</td>
<td>48</td>
<td>18 (23.3)</td>
<td>4.5</td>
</tr>
<tr>
<td>Zen et al. (14) 2017</td>
<td>P</td>
<td>319 (53)</td>
<td>105 patients clinical remission; 34 patient poor adherence</td>
<td>IS</td>
<td>63 (45.3)</td>
<td>91 (53.3)</td>
<td>26 (24.8)</td>
<td>23 (67.6)</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1206 (69.6)</td>
<td></td>
<td></td>
<td>585 (48.5)</td>
<td>284 (56.6)</td>
<td>705.4/58.8</td>
<td>155 (26.5)</td>
<td>2.77</td>
</tr>
</tbody>
</table>

R, retrospective; IS, nonsteroidal immunosuppressant agent; NA, not available; RCT, randomized controlled trial; SLEDAI-2K, SLE disease activity index; P, prospective.

aExcept antimalarial immunosuppressors.

bThe rate flare per year reduced to 1.36 if 23 patients from the study by Zen et al. (14) are included. Those patients voluntarily stopped therapy for poor adherence to prescriptions.
remission, defined by normal serum creatinine, proteinuria <0.5 g/24 h, inactive urine sediment, and no clinical signs of extrarenal activity of SLE for at least 12 months. Twenty-one participants (11%) developed flares during therapy reduction. Treatment reinforcement obtained remission in 20 of 21 patients. The last patient was lost to follow-up at achievement of partial remission. In the remaining 52 participants (26%), immunosuppressive therapy was completely withdrawn. During the subsequent follow-up, 32 patients did not resume immunosuppressive therapy; the other 20 patients had at least one flare, in a median of 37 months after withdrawing therapy, and had to be retreated. After a median follow-up of 24 years, ten of these 20 patients were without therapy (0.8 flares per year) at the last observation, four patients (two without flares and two with flares) died, and two patients who had flares doubled serum creatinine (2.5 and 3 mg/dl, respectively) (Figure 1). Compared with patients with new flares, those who never developed flares received significantly longer treatment (98.1 versus 31.0 months; \( P=0.01 \)), had longer remission before immunosuppression withdrawal (52.8 versus 12.0 months; \( P\leq0.001 \)), and continued hydroxychloroquine after stopping immunosuppressive therapy (52% versus 10%; \( P=0.004 \)). Reduced C3 and C4 complement fractions and high antidouble-stranded DNA antibody titers at the time of withdrawal of therapy did not predict the development of flares. According to a recent study (11), changes in serologic activity are not necessarily associated with the development of new flares. Nevertheless, if after cessation of therapy, patients develop a rapid decrease in complement fractions or higher levels of antidouble-stranded DNA antibodies, strict monitoring is recommended.

These data showed that a gradual discontinuation of therapy is feasible in patients who had received therapy for at least 5 years and are in complete clinical and kidney remission for at least 3 years.

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**Figure 1.** An attempt to interrupt immunosuppressive therapy completely was made in 73 of 161 patients (45%) with lupus nephritis. The participants (class 3, 4, or 5 at kidney biopsy) had to be in stable and complete kidney remission. Immunosuppressive drugs were slowly tapered off, and patients were followed for a mean period of 286 (183–312) months.
Results in Systemic Lupus Erythematosus

Recently, attempts at discontinuing immunosuppressive therapy were made in patients with SLE with or without kidney involvement (Table 1). In a retrospective study, withdrawal of glucocorticoids was made in 91 of 310 patients with SLE (29%). About 50% of patients did not receive immunosuppressive drugs other than glucocorticoids. Seventy-seven patients (25%) could successfully stop glucocorticoids and were followed for 6 years. Eighteen flares (23%) occurred after a median of 1 year in comparison with flares in 70% of 219 patients who continued glucocorticoids. In patients who stopped glucocorticoids, 13 flares were mild and four were kidney flares. Lower-activity SLE activity index scores (median of two [zero to two] versus two [one to four]) and longer time from the last flare (6.0 versus 0.93 years; P<0.001) were associated with lower likelihood of flare after glucocorticoid withdrawal (12). In another study, steroid therapy was gradually tapered off in 148 patients with SLE who were previously in remission; of these participants, 78 had lupus nephritis. Patients received glucocorticoids for a median of 5 years before discontinuation. No other immunosuppressive agent was given in 43% of them. During a median duration of follow-up of 17.9 months, flares developed in 31 patients (21%). Most flares (93%) occurred within the first year in patients who received glucocorticoids ≤8 years versus only 7% flares in patients treated with steroids for >8 years (P=0.009). In multivariable Cox analysis, duration of disease (hazard ratio [HR], 0.89; 95% confidence interval [95% CI], 0.84 to 0.94; P<0.001), duration of glucocorticoids before withdrawal (4.7 versus 6.8 years; HR, 1.00; 95% CI, 1.00 to 1.00; P<0.001), and a second immunosuppressive drug (HR, 1.89; 95% CI, 1.25 to 2.87; P=0.003) were significantly associated with flare-free survival (13). A further attempt was done in 139 (44%) of 319 eligible patients with SLE; 53% had kidney involvement and 45% were not receiving glucocorticoids. Reasons for discontinuation were poor adherence/intolerance in 34 and remission in 105 patients. Remission was defined by SLE activity index equal to zero, stable immunosuppression, prednisone <5 mg/d, and antimalarial therapy. The mean follow-up after drug withdrawal was 91 months. SLE flares occurred in 25% of patients in remission versus 68% of those with poor adherence/intolerance after median follow-up of 57 and 8 months, respectively. These differences were significant. Negative antidualle-stranded DNA antibodies and normal complement fractions did not exert an additional protective effect over clinical remission on flare. Therapy with antimalarials and the duration of remission before discontinuation were independent protective factors against flare. The authors concluded that SLE flares are not uncommon after immunosuppressive therapy discontinuation, even in patients on remission. However, antimalarial therapy and durable remission significantly reduced the risk of flare (14). A small pilot trial included 15 patients in whom prednisone was tapered down to ≤20 mg/d. Participants had class 3 or 4 (plus or minus membranous) lupus nephritis and achieved at least a partial response by cyclophosphamide or mycophenolate. After 3 weeks, prednisone was decreased to 5–7.5 mg/d in eight patients, and that dose was maintained. Prednisone was completely withdrawn in the 17th week in seven patients who were followed for a median of 12 months. Relapse occurred in one patient of the withdrawal group (14%) and in 50% of the low-dose prednisone group. However, the small number of participants and the short duration of follow-up cannot allow us to draw firm conclusions (15).

For a randomized controlled trial, 124 patients with inactive disease during the year before the study who were receiving prednisone 5 mg/d at randomization were admitted to the study. Of them, 61 were randomized to the maintenance treatment, and 63 were randomized to the rapid steroid withdrawal. During a follow-up of 12 months, only four patients (7%) in the maintenance group experienced a flare versus 17 (27%) in the withdrawal group, the difference being significant (risk ratio [RR], 0.2; 95% CI, 0.1 to 0.7; P=0.003). Maintenance of 5 mg prednisone was significantly superior with respect to time to first flare (HR, 0.2; 95% CI, 0.1 to 0.6; P=0.002), occurrence of mild/moderate flares (RR, 0.2; 95% CI, 0.1 to 0.8; P=0.01), and occurrence of moderate/severe flares (RR, 0.1; 95% CI, 0.1 to 0.9; P=0.01). Adverse events were similar in the two groups. The authors concluded that maintenance of long-term low-dose prednisone in patients with SLE and inactive disease prevents relapse (16). Unfortunately, only 21 patients in the maintenance group and 26 in the withdrawal had lupus nephritis. The critical points of the study are the short duration of remission before the interruption of immunosuppressive therapy, the abrupt withdrawal of prednisone, and the lack of placebo.

Repeated Kidney Biopsy

A randomized controlled trial assessed the role of repeated biopsy in predicting flares after immunosuppressive therapy interruption (17) (Table 2). Eligible patients had to be in clinical remission for at least 12 months and had to have received at least 36 months of immunosuppression. Clinical remission was defined by proteinuria ≤500 mg/d, normal kidney function, and inactive urinary sediment. Of 44 enrolled patients, 36 received a second biopsy. Therapy was tapered off over 6 months, and patients were followed for 24 months after repeated biopsy. Nephritics flares occurred in 11 (30%) patients, and all but one showed residual histologic activity on the second biopsy. Duration of SLE and activity index at the second biopsy were independent predictors of flare. The authors concluded that patients in both clinical and histologic remissions may be candidates for therapy withdrawal (17). Despite these impressive results, some issues remain. The above reported studies in lupus nephritis and in SLE suggest that remission longer than 12 months before therapy withdrawal is necessary to reduce flares’ occurrence. However, it is possible or even likely that a longer period of therapy is needed to heal histologic lesions. In a study, complete histologic remission (defined as activity index =0) was documented in 93% of 29 patients with lupus nephritis who received a repeated biopsy >48 months after sustained complete remission (18). Altogether, the small numbers of patients enrolled in these studies do not provide a definitive answer about the need of repeated kidney biopsy. Thus, kidney biopsy may give important pieces of information but is not indispensable to decide whether treatment may be stopped in lupus nephritis.

Malvar et al. (19) moved one step further. They discontinued treatment only in the case of a normal histology at
Table 2. Repeated kidney biopsy as a predictor of kidney flares and of safety withdrawal of therapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. (%) of Patients Recruited/Completed Study</th>
<th>Months of Therapy/Remission before Repeated Kidney Biopsy</th>
<th>No. (%) of Patients with an Activity Index ≥0 at Repeated Kidney Biopsy</th>
<th>Months after Stopping Therapy</th>
<th>No. (%) of Patients Who Developed Kidney Flares</th>
<th>No. (%) of Patients with Activity Index =0</th>
<th>Flare Rate: no./yr</th>
<th>Predictors of Flares</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Rosa et al. (17) 2018</td>
<td>44/36</td>
<td>36/≥12</td>
<td>16 (44.4)a</td>
<td>36 (100)</td>
<td>24</td>
<td>11 (30.5)</td>
<td>1 (9%)</td>
<td>5.5</td>
</tr>
<tr>
<td>Malvar et al. (19) 2019</td>
<td>76/55</td>
<td>42/≥12</td>
<td>20 (26.6)</td>
<td>55 (72.4), all patients with AI=0</td>
<td>50b</td>
<td>7 (12.7)</td>
<td>7 (100)</td>
<td>1.55</td>
</tr>
<tr>
<td>Parodis et al. (21) 2020</td>
<td>42/42</td>
<td>24/NA</td>
<td>10 (23.8)</td>
<td>107.7</td>
<td>0</td>
<td>11 (26.2)</td>
<td>NA</td>
<td>1.23</td>
</tr>
</tbody>
</table>

AI, activity index; R.B., repeated kidney biopsy; NA, not available.
aAI was one or two in nine of 16 patients and three or five in seven patients.
bMycophenolate was withdrawn in 6 months; glucocorticoids were continued beyond year 2 of treatment only if needed for extrarenal SLE activity.

Kidney biopsies performed during therapy. Biopsy was performed in 75 of 220 patients (35%) with class 3 or 4 lupus nephritis who had received immunosuppressive therapy for at least 42 months and had been in remission for at least 12 months. Treatment was withdrawn only if biopsy showed an activity index of zero. Nephritic flares developed within 50 months from the last biopsy in seven of 75 patients (9%) who stopped therapy due to absent histologic activity. This flare rate of 1.5/yr was significantly lower than reported flare rates. No patient developed kidney failure. Four patients developed CKD. The authors concluded that repeated biopsy is safe and may improve the flare rate compared with conventional clinical management (19). However, therapy interruption on the basis of an activity index of zero does not eliminate the likelihood of exacerbation. Patients with activity index greater than or equal to one, severe chronic damage at basal biopsy, rapid progression of kidney disease, and/or poor response to initial therapy were excluded from the study. This negative selection could have influenced the low kidney progression and relapse rate (20). In another study of 42 patients with class 3 or 4 lupus nephritis who received a per-protocol repeat biopsy 24 months after basal biopsy, 11 (26%) relapsed after a median time of 17.9 months from repeated biopsy despite the continuation of therapy. Activity index greater than two and urinary protein-creatinine ratio >1 g/g at repeated biopsy were independent predictors of subsequent kidney relapses (21). The ongoing Per-protocol Repeat Kidney Biopsy in Incident Cases of Lupus Nephritis (REBIOLUP), a prospective multicenter trial aimed to investigate how the prognostic information obtained from control biopsy should assist clinical decisions, may better define the time and the role of repeated biopsy in lupus nephritis (22).

In summary, complete discontinuation of immunosuppressive therapy, including mycophenolate monotherapy, if the patient has been free of relapses for 4 or more years and is in a complete remission is feasible in a selected group of patients. However, it may be burdened by flares of lupus activity in one-third to one-quarter of patients (Figure 2). Flares occur particularly in the period of drug tapering and in the first years after therapy withdrawal. Thus, regular monitoring is mandatory. The prompt reintroduction of glucocorticoids and other immunosuppressants can induce the remission of the kidney and systemic manifestations. The good news is that the three-quarters of patients who do not develop flares enter stable and long-lasting remission with significant improvement in iatrogenic morbidity and quality of life. Before considering immunosuppression withdrawal, some points should be considered. (1) The longer the duration of immunosuppressive therapy is before discontinuation, the better the results are. Hence, it is better to wait for at least 5–6 years before stopping therapy. (2) The ideal candidate for treatment discontinuation should be in complete remission. Persistent clinical signs of lupus activity may be associated with kidney or extrarenal flares after therapy discontinuation. Repeated kidney biopsy may be useful in excluding persistent histologic activity, but it is not mandatory (Table 3). (3) Drugs should be tapered off very gradually under strict surveillance. During an attempt to discontinue treatment, the most delicate phase is represented by treatment reduction (23). (4) Hydroxychloroquine may help to prevent extrarenal flares. (5) In case of kidney flares, a rapid reinstitution of treatment is needed to recover remission and prevent kidney function deterioration. If these cautions are respected, patients with lupus nephritis may discontinue glucocorticoids and other immunosuppressive drugs.

### Benefits of Immune Suppression Withdrawal

Although anti-inflammatory and immunosuppressive drugs may control the disease activity, they can cause side effects and lead to severe comorbidity that can strongly influence life expectancy and quality of life. Usually, inflammatory manifestations and infections are prevalent in the early years after diagnosis of SLE. In the long term, the activity of kidney disease tends to be quenched, but the risks of...
cardiovascular disease, chronic organ damage according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (24), malignancy, and thrombotic events increase.

In SLE, atherosclerosis occurs early in the disease course and progressively aggravates over the time (Figure 3). The atherosclerotic risk cannot be fully accounted for by the higher prevalence of traditional risk factors, but nontraditional risk factors, including immune dysregulation and metabolic disturbances, can also play an important role (25–27). The chronic use of glucocorticoids may aggravate the effects of those risk factors (28,29). Possible mechanisms include hypertension, diabetes mellitus, dyslipidemia, and imbalances in thrombosis and fibrinolysis (30). In SLE, a higher risk of cardiovascular disease is associated with glucocorticoids even at low doses (<5 mg/d prednisone). This

Patients at high risk of flares at therapy withdrawal
- No subsequent therapy after initial therapy
- Frequent relapses
- Persistent active disease
- Short duration of Systemic Lupus Erythematosus
- Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) >4 at stop therapy
- Activity index >2 at repeated kidney biopsy

Patients at low risk of flares after therapy withdrawal
- Longer time since last renal/extrarenal flares
- Longer duration of corticosteroids therapy
- Longer duration of immunosuppressive therapy
- Longer duration of kidney remission
- Use of antimalarials
- Slow and progressive reduction of the drugs
- Strict monitoring of the patients during the reduction of the therapy

Figure 2. | The characteristics of patients who are at high risk and at low risk for stopping immunosuppression.

Table 3. Predictors of flares after withdrawal of immunosuppressive therapy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Clinical Predictors</th>
<th>Therapy Predictors</th>
<th>Histologic Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Rosa et al.</td>
<td>Short duration of SLE at repeated kidney biopsy</td>
<td>Short duration of steroid before stop (4.7 versus 6.8 yr), no treatment with IS; only for kidney flares: lower initial dose of steroids, presence of AIHA</td>
<td></td>
</tr>
<tr>
<td>Goswami et al.</td>
<td>Short duration of SLE at withdrawal of therapy (&lt;8 years)</td>
<td>Activity index &gt;2 at repeated kidney biopsy</td>
<td></td>
</tr>
<tr>
<td>Tani et al.</td>
<td>SLEDAI&gt;4 at stop therapy; short time from last flare (0.93 versus 6 yr)</td>
<td>No use of antimalarial therapy</td>
<td></td>
</tr>
<tr>
<td>Zen et al.</td>
<td>Short duration of remission at stop therapy</td>
<td>Short duration of therapy before stop (2.6 versus 8.2 yr); no use of antimalarial therapy</td>
<td></td>
</tr>
<tr>
<td>Moroni et al.</td>
<td>Short duration of remission at stop therapy (1 versus 4.4 yr)</td>
<td>No use of antimalarials after discontinuation of therapy</td>
<td></td>
</tr>
<tr>
<td>Zen et al.</td>
<td>Younger age at discontinuation of therapy; remission &lt;3 yr at discontinuation of therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IS, immunosuppressor; AIHA, autoimmune hemolytic anemia; SLEDAI, SLE disease activity index.
*The probability of not having a flare is 3.2 times lower for each additional year of steroids administered after remission activity index.
risk is higher if high doses and prolonged courses are used (31). On the other hand, in a long-term study, patients with lupus nephritis who were able to interrupt glucocorticoids and any immunosuppressive therapy had significantly less frequent hypertension (33% versus 67%; \( P < 0.001 \)) and fewer cardiovascular events (12% versus 28%; \( P = 0.04 \)) in comparison with patients who never stopped therapy (10). An important contribution to cardiovascular disease may be given by the prolonged use of calcineurin inhibitors, which may cause hypertension, dyslipidemia, and diabetes (32).

Organ damage is an important issue in patients with SLE. The kidney is a frequent target, especially in patients with lupus nephritis. However, many other organs and systems may be involved, including eyes, central and peripheral nervous systems, lungs, the gastrointestinal system, the musculoskeletal system, and skin. Large analyses of patients with SLE showed that the damage depends on different variables, but hypertension and glucocorticoids are among the strongest predictors of an accrued organ damage (33–36). Patients who interrupted steroid treatment had significantly lower risk of chronic kidney insufficiency (4% versus 28%) and no case of kidney failure in comparison with 13% in patients who never stopped therapy. Flares and chronic organ damage were extremely rare in patients who stopped therapy (8). Moreover, the withdrawal of glucocorticoids reduces the risk of osteopenia and fracture, which are 2.16 times higher in patients who received a dosage of prednisone >7.5 mg/d (37).

In SLE, there is higher risk of hematologic malignancies and other nonhormone-sensitive cancers (38–41). Reduced immunosurveillance may explain the higher risk of malignancy, but high doses or long-term use of cyclophosphamide may exert a direct oncogenic effect, leading to higher rates of bladder cancer, leukemia, lymphoma, and skin malignancies (42–44). Azathioprine is considered as an oncogenic drug as it is incorporated into the DNA of the genome (45). A higher risk of cancer for azathioprine was found in patients with inflammatory bowel disease (46,47). The US Food and Drug Administration warned against the higher risk of lymphoma and skin malignancy. Instead, mycophenolate mofetil is considered an immunosuppressant with antitumor effects by the US Food and Drug Administration. Calcineurin inhibitors can lead to a higher risk of cancer, which is dose and time dependent. This effect is mainly related to their interference with the immune surveillance. Tacrolimus appears to have fewer oncogenic effects than cyclosporin, but it may be associated with a higher risk of tumors when used at high doses (48,49). Few data are available about the use of voclosporin in lupus nephritis (50). However, there is a stable pharmacodynamic profile and a fast elimination of metabolites, resulting in low exposure. Whether this fast elimination will result in a reduced oncogenicity is still unknown.

Regarding severe acute respiratory syndrome coronavirus 2 infections, patients not taking immunosuppressive drugs have a similar risk of symptomatic infection as the general
population (51). On the other hand, the antibody response to the mRNA severe acute respiratory syndrome coronavirus 2 vaccine of kidney transplant recipients was reduced by immunosuppressive therapy (52).

A prominent role in the late complications of SLE is represented by thrombotic events (53). Persistent hypertension, smoking, nephrotic syndrome, and use of glucocorticoids and/or calcineurin inhibitors together with advanced age and the presence of antiphospholipid antibodies can lead to a higher risk of thrombotic events in the long term (54–56). One can speculate that the elimination of glucocorticoids and calcineurin inhibitors may prevent thrombotic events in patients with SLE, but no randomized trials are available to demonstrate this hypothesis.

In conclusion, most of the serious complications of lupus nephritis originate in the early phases when the disease is particularly active and immunosuppressive therapy is aggressive. However, the persistent use of immunosuppressive drugs, even at low doses, may perpetuate and worsen the deleterious effects of these complications and can be responsible for frailty and the poor quality of life of patients (57,58). In the long term, patients with lupus nephritis usually show a low disease activity. This may facilitate a gradual withdrawal of immunosuppressive therapy in selected patients, which can prevent the development of life-threatening and invalidating iatrogenic complications.

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References


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