

March 03/11: Anti-Rib-P probably impacts renal disease course in SLE

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Antibodies to ribosomal P proteins in lupus nephritis: A surrogate marker for a better renal survival?

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Background:

Kidney involvement is a major predictor of poor outcome in systemic lupus erythematosus with 5–10% progression to end-stage renal disease in spite of immunosuppressive therapy. Currently, anti-dsDNA is probably the best available biomarker for lupus nephritis since it correlates well with renal activity, worse prognosis and histology severity. This antibody is not, however, a universal finding in patients with lupus nephritis and therefore there is a need to search for other surrogate markers for long-term outcomes.

Anti-ribosomal P antibodies have emerged as a possible parameter for lupus renal disease since its levels seems to fluctuate in parallel with renal flares and also with disease activity. On the other hand, the authors of this study have reported earlier that SLE patients with isolated anti-P may have a better long-term renal prognosis.

Therefore, the aim of the study was to validate the single antibody specificity of anti-Rib-P as an independent serological marker of good prognosis in renal involvement of SLE.

Summary: Beneath 60 SLE patients with biopsy-proven nephritis 11 (18%) were positive for anti-Rib-P. All 11 were negative for anti-dsDNA. 28 patients (47%) were positive for anti-dsDNA (but negative for anti-Rib-P).

The comparison of the anti-Rib-P-positive group with the anti-Rib-P-negative group revealed a trend to improved renal impairment parameters like lower mean creatinine levels, lower frequency of dialysis, and higher frequency of normal renal function.

Patients with positive anti-dsDNA showed a worse renal survival than double negative SLE patients.

Conclusions: The isolated presence of anti-Rib-P antibodies during nephritis flares is a valuable marker to predict a better long-term renal outcome in lupus patients compared to patients with isolated anti-dsDNA antibodies or absence of both antibodies. Serum creatinine at biopsy is a significant risk factor for end-stage renal failure but anti-Rib-P was more accurate to identify a more favourable prognosis. The anti-dsDNA antibody is able to discriminate lupus renal severity at biopsy and a worse long-term outcome.

Comment: This publication shows that both anti-dsDNA and anti-Rib-P are important markers for the detection of renal involvement in systemic lupus erythematosus and that both markers may give necessary information for an assured prediction of disease course and outcome. This indication enables clinicians to create individual lupus treatment strategies.





Review

Antibodies to ribosomal P proteins in lupus nephritis: A surrogate marker for a better renal survival?

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ABSTRACT

Objective: To define if antibodies to ribosomal P proteins disclose a better lupus nephritis long-term survival. **Methods:** Sixty consecutive SLE patients with biopsy-proven nephritis (2004 ISN/RPS) were evaluated for renal survival parameters. Inclusion criteria were at least one serum sample at: renal flares, biopsy, and last follow-up until 2008. Anti-P was detected by ELISA/immunoblot and anti-dsDNA by indirect immunofluorescence/ELISA.

Results: Eleven patients (18%) with anti-P+ (without anti-dsDNA) during renal flare were compared to 49 (82%) persistently negative for anti-P throughout the study. At the final follow-up post-biopsy (6.3 ± 2.5 vs. 6.8 ± 2.4 years, $p = 0.36$), the comparison of anti-P+/anti-dsDNA– with anti-P– group revealed a trend to lower mean creatinine levels (0.9 ± 0.3 vs. 2.3 ± 2.1 mg/dl, $p = 0.07$), lower frequency of dialysis (0% vs. 35%, $p = 0.025$), and higher frequency of normal renal function (91% vs. 53%, $p = 0.037$). The overall renal survival was significantly higher in anti-P+/anti-dsDNA– compared to anti-P– (11.0 ± 4.5 vs. 9.2 ± 4.5 years, $p = 0.033$), anti-dsDNA+/anti-P– (vs. 8.7 ± 4.7 years, $p = 0.017$), and anti-P–/anti-dsDNA– (vs. 9.8 ± 4.3 years, $p = 0.09$) groups.

Conclusion: Our data supports the notion that anti-P antibody in the absence of anti-dsDNA during nephritis flares is a valuable marker to predict a better long-term renal outcome in lupus patients.

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1. Introduction

Kidney involvement is a major predictor of poor outcome in systemic lupus erythematosus with 5–10% progression to end-stage renal disease in spite of immunosuppressive therapy [1]. Currently, anti-dsDNA is probably the best available biomarker for lupus

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nephritis since it correlates well with renal activity, worse prognosis and histology severity [1]. This antibody is not, however, a universal finding in patients with lupus nephritis and therefore we need to search for other surrogate markers for long-term outcomes.

Anti-ribosomal P antibodies have emerged as a possible parameter for lupus renal disease [2,3] since its levels seems to fluctuate in parallel with renal flares [4–7] and also with disease activity [8–12]. Others have suggested that the immunological determinant of lupus nephritis seemed to be the concomitant occurrence of anti-P with anti-dsDNA antibodies rather than each autoantibody specificity alone [13–15]. We have confirmed and extended this observation demonstrating that the mutual presence of both autoantibodies discriminated patients with membranous glomerulonephritis associated with proliferative lesions [16].

On the other hand, we have reported that isolated anti-P identified a subgroup of patients with pure class V histopathologic pattern [16] raising the possibility that this autoantibody specificity may have a better long-term renal prognosis in SLE. Available studies are, however, retrospective [5], transversal [6,7,10,15] or short-term [4] evaluations which are not accepted outcome measures for renal lupus [17]. Moreover, they have not focused in this single antibody specificity [5,7,15].

We therefore have performed a long-term evaluation of patients with biopsy-proven lupus nephritis and at least one serum sample anti-P positive at the time of renal flares and persistently negative for anti-dsDNA in order to verify if we could validate this single antibody specificity as an independent serological marker of good prognosis in renal involvement of SLE.

2. Patients and methods

2.1. Patients

Eighty-one consecutive SLE (ACR SLE classification criteria) [18] patients who underwent renal biopsy regularly followed at the Lupus Outpatient Clinic from Rheumatology and Nephrology Divisions of São Paulo University Medical School from 1999 to 2004 were selected. All biopsies were reviewed in a blinded manner by the same expert renal pathologist and histological findings were recorded according to the 2004 International Society of Nephrology and the Renal Pathology Society (ISN-RSP) revisited lupus glomerulonephritis classification [19,20]. Inclusion criteria were at least one serum sample at: time of renal flares, biopsy and the last follow-up until 2008. Exclusion criteria were the concomitant presence of anti-P and anti-dsDNA anytime during follow-up ($n=12$); renal injury due to hypertension, diabetes or medications ($n=2$); and those who were unable to present themselves for study follow-up ($n=7$). The Local Ethic Committee approved this study.

Patients' medical records were extensively reviewed for demographic, clinical, therapy, and laboratory data by the same rheumatologist using an ongoing electronic database established in 1999. Disease/nephritis onset and duration were defined according to the time of diagnosis established by the SLE classification criteria [18]. Overall clinical activity was measured according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [21]. The hard end point was defined by death (due to renal involvement or other causes) or the need of chronic dialysis. Plasma creatinine and 24-hours proteinuria were recorded during follow-up. Renal status definitions were based on the Renal Subcommittee of Renal Insufficiency of the American College of Rheumatology [22]. Normal renal function was arbitrarily defined as creatinine ≤ 1.3 mg/dl. End-stage renal disease was defined as the need for dialysis therapy lasting at least 3 months or renal transplant [22].

2.2. Methods

Enzyme-linked immunoassay (ELISA) using purified human recombinant P2 peptide as antigen was employed to detect anti-

ribosomal P protein reactivity. *E. coli*, strain RRI, genetically transformed to produce human P2 polypeptide, was kindly provided by Dr K. Elkon from the University of Washington, Seattle [16]. Antibody reactivity in all sera was confirmed by Western blot technique using purified ribosomal fraction isolated from rat hepatocytes as substrate [23].

Anti-double stranded DNA (dsDNA) antibody was detected by indirect immunofluorescence (IIF) using *Chritidia luciliae* as substrate [24]. All sera were also tested by ELISA using dsDNA preparations from calf thymus (Sigma Chem Co., USA). Results above the mean value of 12 normal sera plus 5 SD were considered positive. To ensure the specificity of antibodies to dsDNA positive sera were further checked onto sensitized plates treated for 1 h at 37° with S1 nuclease (500 UI/ml) (Sigma Chem. Co., St. Louis, USA) prior to the addition of serum samples [16].

2.3. Statistical analysis

Results are presented as the mean \pm standard deviation (SD) for continuous and number (%) for categorical variables. Data were compared by *t* test, Mann–Whitney U tests or Wilcoxon rank sum tests in continuous variables to evaluate differences among groups. For categorical variables differences were assessed by Pearson Chi-Square or Fisher's Exact Test. Renal survival analysis – the length of time to ESRD or renal related death – and overall patient survival was performed using Kaplan–Meier procedure, and log-rank test statistics. Statistical significance was set as $P < 0.05$.

3. Results

Sixty SLE patients with nephritis were evaluated according to the inclusion and exclusion criteria. The frequency of anti-P anytime during follow-up in renal flares was 18% ($n=11$) comprising the anti-P+/anti-dsDNA– group. The remaining 49 patients (anti-P– group) were persistently negative for this antibody during the entire follow-up.

At the time of biopsy, demographic evaluation of SLE patients with and without anti-P antibodies revealed a similar female gender ($p=0.58$) and white race ($p=0.74$) distribution (Table 1). The mean age at biopsy was also alike in both groups ($p=0.86$). In addition, patients with and without anti-P antibodies had a comparable mean

Table 1

Demographics, clinical findings and follow-up of 60 lupus nephritis patients with and without anti-P antibodies.

	Anti-P+/anti-dsDNA– ($n=11$)	Anti-P– ($n=49$)	<i>P</i>
At biopsy			
Female, n(%)	11 (100)	43 (88)	0.58
White, n(%)	6 (54)	30 (61)	0.74
Age, years	31.8 \pm 10.0	32.1 \pm 10.3	0.86
SLE Disease duration, years	6.4 \pm 6.9	2.8 \pm 3.5	0.048
Renal disease duration, years	2.4 \pm 4.9	1.7 \pm 2.7	0.57
Creatinine, mg/dl	1.0 \pm 0.3	2.3 \pm 1.6	0.001
Proteinuria, g/24 h	5.9 \pm 3.1	6.0 \pm 5.9	0.30
Class IV, n(%)	2 (18)	33 (67)	0.005
Class V, n(%)	10 (91)	15 (31)	<0.001
Proliferative lesions, n(%)	5 (45)	40 (82)	0.021
SLEDAI	10.4 \pm 3.9	9.0 \pm 4.3	0.16
At follow-up			
Period of follow-up, years	6.3 \pm 2.5	6.8 \pm 2.4	0.36
Normal renal function, n(%)	10 (91)	26 (53)	0.037
Final creatinine, mg/dl	0.9 \pm 0.3	2.3 \pm 2.1	0.07
Dialysis, n(%)	0 (0)	17 (35)	0.025
Final proteinuria, g/24 h	1.0 \pm 1.6	2.5 \pm 4.5	0.11
Overall survival, years	13.6 \pm 6.1	11.5 \pm 4.5	0.23
Renal survival, years	11.0 \pm 4.5	9.2 \pm 4.5	0.033
Renal related death, n(%)	0 (0)	6 (12)	0.58

Values are expressed in mean \pm SD or percentage.

duration of renal disease (2.4 ± 4.9 vs. 1.7 ± 2.7 years, $p = 0.57$) in spite of a longer duration of lupus (6.4 ± 6.9 vs. 2.8 ± 3.5 years, $p = 0.048$) (Table 1). Anti-P+/anti-dsDNA– patients had a significant lower creatinine levels compared to anti-P negative patients (1.0 ± 0.3 vs. 2.3 ± 1.6 mg/dl, $p = 0.001$), whereas proteinuria levels and SLEDAI scores were similar among groups (5.9 ± 3.1 vs. 6.0 ± 5.9 g/24 h, $p = 0.30$ and 10.4 ± 3.9 vs. 9.0 ± 4.3 , $p = 0.16$; respectively). The frequency of proliferative lesions at biopsy was higher in patients with anti-P negative group compared to the other group (82% vs. 45%, $p = 0.021$). Moreover, the frequency of class V nephritis was higher in anti-P+/anti-dsDNA– group (91% vs. 31%, $p < 0.001$) whereas the frequency of class IV was lower compared to the anti-P– (18% vs. 67%, $p = 0.005$) (Table 1).

The post-biopsy follow-up analysis demonstrated that both groups had a similar period of observation until 2008 (6.3 ± 2.5 vs. 6.8 ± 2.4 years, $p = 0.36$). The renal assessment at this last follow-up revealed a higher frequency of normal renal function in the anti-P+/anti-dsDNA– group (91% vs. 53%, $p = 0.037$) and a trend of lower mean creatinine levels (0.9 ± 0.3 vs. 2.3 ± 2.1 mg/dl, $p = 0.072$). Reinforcing this finding, none of the anti-P+/anti-dsDNA– patients underwent dialysis while more than a third of the anti-P– required this treatment (0% vs. 35%, $p = 0.025$) (Table 1). No significant differences were detected among anti-P+/anti-dsDNA– and anti-P– regarding treatment with cyclophosphamide (54% vs. 69%, $p = 0.48$) or mycophenolate mofetil (27% vs. 8%, $p = 0.10$). The overall renal survival from disease diagnosis was significantly longer in anti-P+/anti-dsDNA– patients compared to other group (11.0 ± 4.5 vs. 9.2 ± 4.5 years, $p = 0.033$) (Fig. 1) in spite of a comparable overall lupus survival from diagnosis in both groups (13.6 ± 6.1 vs. 11.5 ± 4.6 years, $p = 0.23$) (Table 1).

The comparison of anti-P+/anti-dsDNA– patients with the 28 patients with positive anti-dsDNA and negative for anti-P disclosed that the former had at the final follow-up lower creatinine levels (0.9 ± 0.3 vs. 2.6 ± 2.3 mg/dl, $p = 0.037$), higher frequency of normal renal function (91% vs. 43%, $p = 0.001$), lower frequency of dialysis (0% vs. 43%, $p = 0.009$) (Table 2), and longer overall renal survival (11.0 ± 4.5 vs. 8.7 ± 4.7 years, $p = 0.017$) (Fig. 1).

The subsequent analysis of anti-P+/anti-dsDNA– patients and 21 patients double negative (absence of anti-P and anti-dsDNA) revealed a lower creatinine levels at the time of biopsy (1.0 ± 0.3 vs. 2.1 ± 1.7 mg/dl, $p = 0.008$) and a tendency of higher overall renal survival (11.0 ± 4.5 vs. 9.8 ± 4.3 years, $p = 0.09$) in the former group (Fig. 1).

The cumulative renal survival was significantly better in patients with anti-P+/anti-dsDNA– compared to patients without this antibody ($p = 0.033$), patients with anti-dsDNA+/anti-P– ($p = 0.017$)

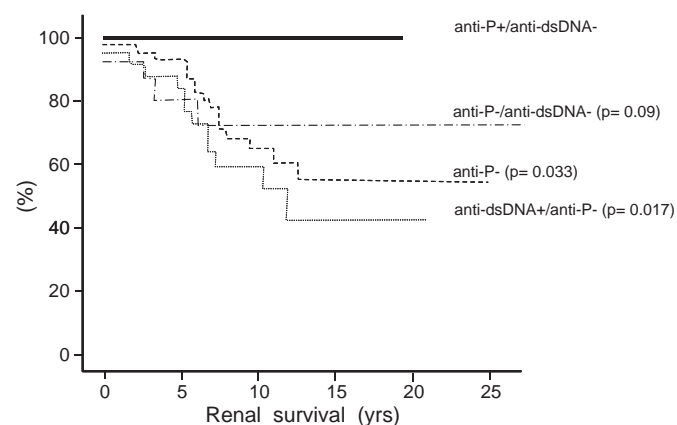


Fig. 1. Renal survival of SLE patients. Kaplan-Meier analysis of renal related death as the end point. Comparison of anti-P+/anti-dsDNA– with: anti-P– ($p = 0.033$); anti-dsDNA+/anti-P– ($p = 0.017$); anti-P–/anti-dsDNA– ($p = 0.09$).

Table 2

Demographics, clinical findings, and follow-up in patients with isolated anti-P and anti-dsDNA antibodies.

	Anti-P+/anti-dsDNA– (n = 11)	Anti-dsDNA+/anti-P– (n = 28)	P
At biopsy			
Female, n(%)	11 (100)	24 (86)	0.31
White, n(%)	6 (54)	16 (57)	1.00
Age, years	31.8 ± 10.0	30.7 ± 8.5	0.54
SLE disease duration, years	6.4 ± 6.9	2.6 ± 2.9	0.09
Renal disease duration, years	2.4 ± 4.9	1.8 ± 2.6	0.86
Creatinine, mg/dl	1.0 ± 0.3	2.4 ± 1.6	0.001
Proteinuria, g/24 h	5.9 ± 3.1	5.1 ± 4.3	0.18
Class IV, n(%)	2 (18)	20 (71)	0.004
Class V, n(%)	10 (91)	8 (29)	0.001
Proliferative lesions, n(%)	5 (45)	24 (83)	0.017
SLEDAI	10.4 ± 3.9	9.6 ± 4.6	0.41
At follow-up			
Period of follow-up, years	6.3 ± 2.5	6.7 ± 2.7	0.41
Normal renal function, n(%)	10 (91)	12 (43)	0.001
Final creatinine, mg/dl	0.9 ± 0.3	2.6 ± 2.3	0.037
Dialysis, n(%)	0 (0)	12 (43)	0.009
Final proteinuria, g/24 h	1.0 ± 1.6	2.4 ± 4.5	0.11
Overall survival, years	13.6 ± 6.1	11.0 ± 4.6	0.20
Renal survival, years	11.0 ± 4.5	8.7 ± 4.7	0.017
Renal related death, n(%)	0 (0)	4 (14)	0.31

Values are expressed in mean \pm SD or percentage.

and a tendency in patients with double negative antibodies (anti-P–/anti-dsDNA–) ($p = 0.09$) (Fig. 1).

4. Discussion

This is the first study to identify anti-ribosomal P antibodies as a possible surrogate marker of a better long-term renal lupus survival.

The long-term follow-up using chronic renal impairment parameters is the foremost strength of the present report since these measures are accepted as a more relevant outcome assessment for lupus glomerulonephritis than short-term evaluations as demonstrated in the original National Institute of Health trials for renal involvement in lupus [17]. The comparable distribution among groups regarding gender is another important aspect since data accumulated during the years provided substantial evidence that sex hormones influence B cells maturation and selection [25] and may account for more severe lupus nephritis in male patients [26]. Likewise, the balanced distribution of race minimized the previously described impact of race/ethnicity on SLE severity [27].

The frequency of anti-P observed herein is similar to our previous report [16] and lower than that observed in children [28], oriental [29,30], and African American SLE populations [30]. Of note, all patients positive for anti-P had this reactivity at renal flares, reinforcing previous finding that this antibody is associated with active disease [4–7,29].

The comparable renal disease duration is a relevant issue taking into consideration the accrual damage over time [31] since it allowed a similar exposure period for patients with isolated anti-P (anti-P+/anti-dsDNA–) and those without this antibody. Likewise the duration of the follow-up post-biopsy was also equivalent in both groups and revealed that renal parameters were significantly better in patients with isolated anti-P (anti-P+/anti-dsDNA–). At the final evaluation, the great majority had normal function and none underwent dialysis.

Reinforcing these findings patients with single anti-P antibodies (anti-P+/anti-dsDNA–) during renal flare compared to those with isolated anti-dsDNA (anti-dsDNA+/anti-P–) have an even more impressive better renal outcome. Indeed, we have confirmed that anti-dsDNA antibody is able to discriminate lupus renal severity at biopsy and a worse long-term outcome [1]. Treatment did not influence these findings since no difference was detected among groups. On the

other hand we have demonstrated that the good prognosis associated with isolated anti-P (anti-P+/anti-dsDNA-) is not simply related to the absence of anti-dsDNA, since the group of patients double negative (anti-P-/anti-dsDNA-) had also a tendency of worse renal survival than patients with isolated anti-P (anti-P+/anti-dsDNA-).

A protective role for autoantibodies in the pathogenesis of lupus nephritis has rarely been reported in the literature and is restricted to a few studies suggesting that the presence of rheumatoid factor was associated to the formation of more heavily sedimenting immune precipitates which would be less likely to deposit in the renal glomeruli but these data remain controversial [32,33]. In the present study, patients with isolated anti-P (anti-P+/anti-dsDNA-) were selected for renal involvement excluding therefore any consideration regarding a protective effect.

In our previous observation that single anti-P antibodies reactivity was associated with 2004 ISN-RSP class V histological pattern might suggest that the most likely explanation for the good outcome observed herein was merely the low frequency of progression to end-stage renal disease observed in patients with membranous lupus nephritis [34,35]. On the contrary, approximately half of the patients displayed class V as an additional diagnosis in the setting of lupus nephritis class III or IV. In fact, the presence of endocapillary involvement at biopsy did not fully predict the long-term outcome.

We have confirmed that serum creatinine at biopsy is a significant risk factor for end-stage renal failure [1,36,37] but anti-P was even more accurate to identify the more favorable prognosis, since among the three anti-P+/anti-dsDNA- patients with high creatinine levels at biopsy, two improved to normal renal function and one remained stable. In any case, isolated anti-P (anti-P+/anti-dsDNA-) at biopsy in patients persistently negative for anti-dsDNA seemed to constitute a relevant parameter of excellent renal survival.

5. Conclusion

Our data supports the notion that anti-P antibody in the absence of anti-dsDNA during nephritis flares is a valuable marker to predict a better long-term renal outcome in lupus patients.

Take-home messages

- Isolated anti-P antibodies in nephritis flares predict a very good long-term renal outcome in lupus patients.
- Isolated anti-P has a better nephritis long-term survival than isolated anti-dsDNA or absence of both antibodies.

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Methotrexate in patients with primary biliary cirrhosis who respond incompletely to treatment with ursodeoxycholic acid.

Primary biliary cirrhosis (PBC) is an autoimmune chronic liver disease that affects mostly women over the age of 40 years. The disease is characterized by cholestasis, the presence of anti mitochondrial antibodies (AMA), inflammation and destruction of intrahepatic bile ducts. PBC patients are commonly treated with ursodeoxycholic acid (UDCA) to ameliorate the cholestatic liver diseases. However, up to 35% of PBC patients have progressive disease despite this therapy (i.e. persistent hepatitis or more than 50% elevation of alkaline phosphatase after 12 months). In a recent study Marshal M Kaplan et al. (*Digestive Disease* 55(11):3207–3217) offered treatment with colchicine and methotrexate to 91 patients who failed to respond adequately to UDCA. Treatment was initiated with colchicine and if no decrease in alkaline phosphatase levels was observed after 6 months methotrexate was added. The addition of methotrexate to colchicine resulted in a significant decrease in mean levels of alkaline phosphates and ALT. Moreover, serial biopsies confirmed decrement in liver inflammation scores following 12 months of therapy. Thus, the authors concluded that a combination therapy with colchicine and methotrexate can effectively improve liver enzymes tests and liver histology among PBC patients who fail to respond to UDCA. **Nancy Agmon-Levin.**

Interleukin-6 and systemic lupus erythematosus: another bullet, another target

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by frequent renal involvement, the so called “lupus nephritis”. The pathogenesis is complex and requires the intervention of several pro-inflammatory molecules within which are immune complexes, growth factors, chemokines and cytokines. Interleukin-6 (IL-6) is a pleiotropic cytokine with a range of biological activities. Furthermore, it is the main activator of the acute phase response in liver. Moreover, high levels of this cytokine have been found in patients with several autoimmune diseases, such as rheumatoid arthritis and SLE as well. Similarly, mouse models show high levels of the cytokine, especially in the case of renal disease. Blocking the molecule resulted in improved disease evolution, while overexpression in worsening of the histopathological course with development of mesangial proliferation. For this reason, recently Cash and coworkers (*J Rheumatol*. 2010;37:60–70) created IL-6 deficient MRL-Fas^{lpr} mice, aiming at evaluating the evolvement of lupus nephritis. Relevantly, these mice showed a milder course of the disease and a reduced mortality. The mice had a delay in the clinical manifestations, a longer lifespan and even the bioptical findings showed a diminishment in the infiltrating cells in kidneys. Likewise, the effects of IL-6 deficiency were evident at a genetic level, with downregulation of several genes involved in inflammation, such as those encoding for ROR t (Th17), Gata-3 and STAT4. This study adds another dowel to the mosaic of autoimmunity, demonstrating that IL-6 has a role – and a strong one – in the development of lupus nephritis. Watching carefully at the encouraging results achieved by IL-6 blocking agents in human SLE, it is time to hope to hit the bull's eye in SLE treatment. **Carlo Perricone, M.D.**

Ciclosporin versus azathioprine: old battles and new challenges

In the treatment of Systemic lupus erythematosus (SLE) not many randomized controlled trials (RCTs) have been conducted so far, besides the fact that treating severe SLE remains unsatisfactory. Only recently, pharmaceutical companies are starting to perform RCTs to evaluate the new biological therapies in this group of patients. Severe SLE often requires high doses of corticosteroids, thus, there is a pressing need for corticosteroid-sparing agents added to reduce the risk of long-term toxicity from corticosteroids. Azathioprine (AZA) has been the first drug with corticosteroid-sparing potentials used in SLE treatment. More recent is the experience with ciclosporin (CyA), since the role played by T cells in the disease development and progression has been widely demonstrated. Besides the fact that it now several years that CyA has been introduced in SLE treatment, only in 2010 Griffiths and colleagues (*Rheumatology (Oxford)*. 2010;49:723–32) undertook an RCT to evaluate the role of this drug as a corticosteroid sparing agent compared with AZA. Both drugs achieved the primary end point with a reduction of > 50% of the mean dose of prednisolone at 12 months. On the other side, they showed a very high failure rate that accounted for nearly 50% of patients treated. On the light of these data, CyA may be considered a valid alternative to AZA, even in patients with severe SLE. However, there is the strong feeling that new, safer and more effective drugs are required in the treatment of SLE. **Carlo Perricone, M.D.**