

## Lupus Nephritis: current concepts

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*Lupus nephritis (LN) is a common and ominous manifestation of systemic lupus erythematosus (SLE). It affects more than 50 percent of SLE patients, and in case of severe form it can lead to renal failure and death. The renal flare commonly occurs within years after the first episode. Frequent monitoring for renal flare enhances early recognition and timely treatment. The mainstay therapy remains a prolonged use of cytotoxic/immunosuppressive drugs, which contains a number of undesirable effects, particularly infection and ovarian failure.*

*In this review, we highlight recent understandings in the pathogenesis of LN and the development of latest immunosuppressive agents directed against specific molecular targets, which enable more treatment options.*

**Keywords :** *Lupus nephritis, Glomerulonephritis, Systemic lupus erythematosus, Immunosuppression, Mycophenolate, Anti-CD40 Ligand, LJP-394*

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### Objective

1. To review current update in the pathogenesis, clinicopathologic correlation and management of lupus nephritis patients.
2. To review the current immunosuppressive agents as well as novel agents for the future treatment of the disease.

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**ยิ่งยศ อวิหิงसानนท์, ญัฐฐิยา พิมพ์โนนทัย, สมชาย อรรถศิลป์. ความรู้ใหม่เกี่ยวกับภาวะไต  
อักเสบจากโรคอุปฺส. จุฬาลงกรณ์เวชสาร 2547 มิ.ย: 48(6): 387 - 403**

ภาวะไตอักเสบจากโรคอุปฺสเป็นภาวะที่เกิดขึ้นได้บ่อย และมักจะมีควมรุนแรงมากในผู้ป่วยที่เป็นโรคอุปฺสหรือโรคเอสแอลอี โดยมากกว่าร้อยละ 50 ของผู้ป่วยจะเกิดมีไตอักเสบซึ่งอาจนำไปสู่ภาวะไตวายหรือเสียชีวิตได้ ภาวะนี้สามารถเกิดซ้ำได้ตั้งนั้นการเฝ้าระวังการกำเริบของโรคสามารถทำให้วินิจฉัยได้รวดเร็วและให้การรักษาได้อย่างทันท้วงที ซึ่งปัจจุบันการรักษาด้วยยากดภูมิคุ้มกันยังคงเป็นยาหลักถึงแม้ว่ายาในกลุ่มนี้มีผลข้างเคียงค่อนข้างมาก โดยเฉพาะการติดเชื้อและทำให้มีบุตรยาก

ในบทความนี้ ได้ทบทวนความรู้ใหม่เกี่ยวกับพยาธิกำเนิด และยากดภูมิคุ้มกันใหม่ ซึ่งมีการออกฤทธิ์จำเพาะต่อโมเลกุลเป้าหมาย ทำให้แพทย์มีทางเลือกมากขึ้นในการใช้ยารักษาโรคนี้

**คำสำคัญ :** ภาวะไตอักเสบจากโรคอุปฺส, ภูมิคุ้มกันต่อเนื้อเยื่อตนเอง, เอสแอลอี, ยากดภูมิคุ้มกัน, มัยโคฟีโนเลต

Renal disease is a common and serious manifestation of systemic lupus erythematosus (SLE). Its presentation can range from asymptomatic urinary abnormalities to rapidly progressive renal failure leading to end-stage renal disease. The overall mortality rate in Thailand has improved since 1986.<sup>(1)</sup> The 5-year survival rate, as recently reported by Shayakul *et al*, were 76.5 percent which is comparable to that of the Western countries.<sup>(2,3)</sup> This continuing improvement may reflect the early diagnosis and treatment, together with a better understanding of the pathogenesis of the disease and refinement of supportive cares, i.e. treatment of infection, hypertension and renal replacement therapy.

Despite continued improvement of the outcomes, renal failure and death remain major issues among the patients with lupus nephritis (LN). Currently available immunosuppressive regimens are somewhat toxic due to their broadly immunosuppressive effects. Cyclophosphamide plus prednisolone have become the standard regimen for severe form of LN. Since SLE usually affects women of child-bearing age, this regimen results in serious adverse effects in these patients, especially gonadal toxicity. Evidences from randomized-controlled trials support the use of cyclophosphamide as an induction of remission therapy. This drug appears to have some advantages in early therapeutic response which leads to a dramatic improvements of long-term outcomes.<sup>(4)</sup>

Our understanding in the pathogenesis of SLE and autoimmunity enable direct treatment to specific targets. There are recent progresses in LN treatment with agents that have evolved from immunobiology and organ transplantation. These agents have more specific immunosuppression and include monoclonal

antibodies directed against immune cells, cytokines and components of the complement system<sup>(5)</sup> (reference 5 for review). This review covers current understanding in immunopathogenesis of LN and its novel therapeutic regimens.

### Pathogenesis

SLE is an autoimmune disease with a complex pathogenesis driven by interaction between environmental factors and genetically determined abnormalities of the immune system.<sup>(6)</sup> The immune dysregulation is characterized by polyclonal B-cell activation and the formation of autoreactive antibodies directed against nuclear antigen and other self-antigen.<sup>(7)</sup> These autoantibodies can cause organ injury by direct antigen recognition on target cells, as in autoimmune hemolytic anemia. Alternatively, immune complex can bind complement and deposit or they can be formed *in situ*. They subsequently cause damage in the kidney by activation of the humoral and cellular mediators of the inflammatory cascade and by the direct binding of highly positive charged nuclear histone antigen and anti-DNA antibodies to the negatively charged glomerular basement membrane, thereby altering glomerular function and permeability. Although polyclonal B-cell hyperactivity might suggest that autoantibody production is induced through nonspecific stimulation, in fact it now appears that autoantibodies are induced by cognate autoreactive helper T-cells.<sup>(8)</sup> Multiple cytokines including interleukins, platelet activating factor, and monocyte chemoattractant protein have been implicated in the pathogenesis of LN.<sup>(9)</sup> This improved understanding of the pathogenesis of LN is leading to more specifically

targeted treatment for LN.

### Genetic susceptibility

Although cumulative evidence suggests that a genetic predisposition plays a major role in the development of SLE and/or LN, the susceptibility genes are mostly unknown. The difficulty in identifying the susceptibility genes is because they are multiple genes with variable genetic effects and the diverse genetic backgrounds of human populations.<sup>(10)</sup> In human SLE, genes of early components of complements as well as many polymorphic genes (including the MHC class II and class III, FcγR, mannose-binding protein, IL-6, Bcl-2, and IL-10 genes) have been associated with SLE or LN by population-based case-control or within-case studies.<sup>(11)</sup> The contribution of some of these disease-associated genes to the presence or absence of clinical manifestations has been further tested in mice with targeted disruption of the specific candidate genes.<sup>(12)</sup>

The availability of densely mapped genetic markers spanning the entire genome has enabled the identification of chromosomal regions linked to disease susceptibility genes without prior knowledge of the gene function. Evidence for linkage of a chromosome 1q41-42 region was observed in SLE-affected sib pairs from multiple ethnic groups.<sup>(13)</sup>

### The roles of autoreactive B cells

In addition to the function of antibody production, B-cells are important antigen-presenting cells for CD4+ T cells. A clear demonstration for the role of B cells in murine LN was observed when the B-cell inactivation mutation was bred onto the MRL/

lpr lupus background. Mice with the mutation lacked B-cells and did not develop any manifestation of nephritis.<sup>(14)</sup> B-cells not only promote and expand normal T-cells, they also serve as antigen-presenting cells for activation of autoreactive T-cells. These effects are mediated through major histocompatibility complex class II, and costimulatory molecules. B-cell deficient MRL/lpr mice have reduced a number of spontaneously activated and memory CD4+ T cells. Evidently, T-cells activated in the absence of B-cells are either too few or lacking key autoreactivities to promote sustained disease.

### The roles of cellular immunity

Cellular immune mechanisms have recently begun to receive increased attention in LN. Immunohistochemical analysis demonstrates significant infiltration of T cells and macrophages in the kidney of lupus patients, suggesting a role of these cells in the initiation and progression of LN.<sup>(8,15)</sup> Increased expression of class II MHC molecules and CD40 on renal tubular epithelial cells<sup>(16)</sup>, in addition to upregulation of CD40L and IL-2 receptor on infiltrating T cells, indicate that cellular immune responses are essential components of LN.<sup>(17)</sup> Whether or not these infiltrating T-cells recognize antigens in the interstitium remains unclear. Chemotactic factors, especially MCP-1, and adhesion molecules, such as ICAM-1, cooperatively facilitate recruitment of mononuclear cells into inflamed tissue.<sup>(18)</sup> Initial data suggest the importance of cell-to-cell contact-mediated direct tissue injury in the kidney and have provided new candidates for specific immune therapy. In this context, blocking the CD40-CD40L pathway is particularly attractive because, in addition to its role

in autoantibody production, the CD40-CD40L pathway may also be involved in direct cell-to-cell interactions.

### Type of renal disease

Renal biopsy provides unique information in addition to clinical data because glomerular lesions in LN are related to the patient and renal outcomes. The World Health Organization (WHO) pathologic classification of LN, based upon the extent and severity of glomerular inflammation, has been a

cornerstone of the study and treatment of LN. (Table 1) Diffuse proliferative lesion (type IV) is the most common and the most severe form of LN. Mesangial (type II) and membranous (type V) types are mild form and have relatively normal renal function. Focal proliferative type (type III) has quite variable clinical features. Progressive renal dysfunction is uncommon in type III with less than 25 percent of glomerular involvement.<sup>(19)</sup>

**Table 1.** World Health Organization (WHO) morphologic classification of lupus nephritis (modified in 1982).

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#### Class I Normal glomeruli

- a. Nil (by all techniques)
- b. Normal by light microscopy, but deposits by electron or immunofluorescence microscopy

#### Class II Pure mesangial alterations (mesangiopathy)

- a. Mesangial widening and/or mild hypercellularity
- b. Moderate hypercellularity

#### Class III Focal segmental glomerulonephritis (associated with mild or moderate mesangial alterations)

- a. With "active" necrotizing lesions
- b. With "active" and sclerosing lesions
- c. With sclerosing lesions

#### Class IV Diffuse glomerulonephritis (severe mesangial, endocapillary or mesangiocapillary proliferation and/or extensive subendothelial deposits)

- a. Without segmental lesions
- b. With "active" necrotizing lesions
- c. With "active" and sclerosing lesions
- d. With sclerosing lesions

#### Class V Diffuse membranous glomerulonephritis

- a. Pure membranous glomerulonephritis
- b. Associated with lesions of class II
- c. Associated with lesions of class III
- d. Associated with lesions of class IV

#### Class VI Advanced sclerosing glomerulonephritis

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Several studies have emphasized the usefulness of semiquantitative analysis to assess the activity and chronicity of nephritis.<sup>(19,20)</sup> The maximum of activity score is 24 and the maximum of chronicity score is 12. The score may be used as a prognostic index. However, the value of the index and its

reproducibility is uncertain. Recently, the latest classification modified from the WHO classification has been proposed. (Table 2) This new classification claimed the reproducibility and correlation to the long-term outcome.<sup>(21)</sup>

**Table 2.** International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis.<sup>(21)</sup>

<b>Class I</b>	<b>Minimal mesangial lupus nephritis</b> Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
<b>Class II</b>	<b>Mesangial proliferative lupus nephritis</b> Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
<b>Class III</b>	<b>Focal lupus nephritis<sup>a</sup></b> Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving < 50 % of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions : focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
<b>Class IV</b>	<b>Diffuse lupus nephritis<sup>b</sup></b> Active or inactive diffuse, segmental or global endo-or extracapillary glomerulonephritis involving > 50 % of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when > 50 % of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when > 50 % of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation

**Table 2. Continue.**

Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis Active and chronic lesions; diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
<b>Class V</b>	<b>Membranous lupus nephritis</b>  Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy , with or without mesangial alterations  Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed  Class V lupus nephritis show advanced sclerosis
<b>Class VI</b>	<b>Advanced sclerosis lupus nephritis</b>  ≥ 90 % of glomeruli globally sclerosed without residual activity

<sup>a</sup> Indicate the proportion of glomeruli with active and with sclerotic lesions.

<sup>b</sup> Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

### Indication for renal biopsy

Renal biopsy is a valuable tool in the diagnosis, and prognosis as well as therapeutic guidance of SLE patients. Clinical features are often correlated with renal pathologies. More severe histological forms of nephritis have more severe clinical manifestations and even though correlations are present, renal histology cannot be predicted with any certainty from the clinical pictures. Moreover, so-called silent nephritis was commonly found in a number SLE patients without clinical renal involvement.<sup>(22)</sup> Mild proteinuria, hematuria and proteinuria with bland urine sediment are non-specific

findings. These can be found in focal or diffuse proliferative lesions or membranous type. Patients with acute renal insufficiency, active urine sediments (red blood cells and red blood cell casts) and active serology (low complement and high anti-dsDNA titer) almost always have active proliferative lesions (WHO class IV). Therefore, immediate treatment without histological confirmation is reasonable for this specific presentation. However, severe renal pathology, such as crescentic lesions and thrombotic microangiopathy, cannot be excluded. Taken all the information together, renal biopsy is recommended in most SLE patients

with clinically renal involvement. Moreover, repeated biopsies may be required in late progression of renal disease to distinguish between active lupus (which may require immunosuppressive therapy) and scarring of previous inflammatory injury (which may warrant antihypertensive therapy with angiotensin converting enzyme inhibitor). Regarding the multi-organ system involvement of SLE, we should be cautious for the contraindications of renal biopsy e.g. thrombocytopenia, severe hemolytic anemia and uncontrolled hypertension.

### **Treatment of severe lupus nephritis**

The optimal treatment of LN varies with the type of renal pathology. In this review, we will concentrate on the treatment of diffuse or severe focal proliferative glomerulonephritis (type III or IV). Indeed, we are dealing with two distinct therapeutic problems; first is the induction treatment of severe and acute life-threatening disease of which the immunosuppressive treatment is paramount; second is the maintenance treatment and long-term management during which protection from the relapse of disease and the side effects of treatment becomes more important.

### **Induction treatment**

It is important to note that the 5-year survival, free of renal failure or death, for this group of patients is still no better than 75-80 percent. Thus, there is a great deal of room for improvement in the overall results. The majority of morbid events among these patients appear early in the course of disease. The initial treatment to induce remission has been shown to improve the long-term outcome.<sup>(4,23)</sup>

### **Cyclophosphamide as a current standard treatment**

The evidences indicate that treatment with high-dose prednisolone (1-2 mg/kg/day) plus an immunosuppressive agent is more effective than prednisolone alone.<sup>(23)</sup> Cyclophosphamide (CY), an alkylating agent of which action is to inhibit DNA replication and transcription, was introduced to treat LN since 1960. The intermittent pulse intravenous cyclophosphamide (IVCY) seems to have the best therapeutic effect, reducing the mortality and risk of ESRD. Two prospectives, randomized controlled trials, performed by the National Institute of Health (NIH), as well as the recent meta-analysis, support the efficacy of IVCY over that of pulse methylprednisolone or prednisolone alone.<sup>(24,25)</sup> Combination of pulse methylprednisolone and IVCY may even have better outcome.<sup>(26,27)</sup> However, there is an increasing cost of adverse effects from immunosuppression particularly opportunistic infection. We prefer to use intermittent pulse IVCY for severe LN patients at our institute (Table 3). In addition to the NIH cohort, the efficacy of IVCY has been proved among Thai patients with severe LN.<sup>(2)</sup>

### **Different dosing regimens of cyclophosphamide**

Several investigators raised some concerns over the indiscriminate use of the so-called "NIH regimen" in the treatment of all LN patients.<sup>(28)</sup> Firstly, high-dose IVCY treatment is highly toxic; up to 25 % of patients develop herpes zoster infection; up to 26 % experience severe infection; and up to 52 % of women are at risk of having ovarian failure.<sup>(23)</sup> Secondly, clinically milder cases of biopsy-proved proliferative nephritis for which less aggressive



**Table 3.** Intermittent pulse intravenous cyclophosphamide therapy (modified from Austin HA et al).<sup>(37)</sup>

1. Administer pulse cyclophosphamide (IVCY) monthly for 6 months. Can infuse IVCY every 3 weeks in patients with extremely aggressive disease. Then infuse IVCY quarterly for 18 months or 1 year beyond remission
2. Initial IVCY dose is 0.75 g/m<sup>2</sup> (0.5 g/m<sup>2</sup> if GFR < one-third normal). Adjust subsequent dose to maximum of 1 g/m<sup>2</sup> unless WBC nadir at 10 or 14 days after IVCY falls below 1500 mm<sup>3</sup>.
3. Induce dilute diuresis by large volume of oral water intake and frequent voiding for 24 hours after IVCY.
4. Give antiemetic i.e. metoclopramide or ondansetron for 24-48 hours after IVCY.
5. prednisolone dose: 0.5 mg/kg/day for 4 weeks followed by tapering to 0.25 mg/kg every other day.

treatment might be justified are now frequently diagnosed because of prompt assessment of early renal involvement.

The Euro-Lupus Nephritis Trial (ELNT)<sup>(29)</sup> is a multicenter, prospective, randomized study designed to compare a low-dose IVCY regimen (6 fortnightly pulses of 500 mg; cumulative dose 3 gm) with a high-dose IVCY treatment therapy for proliferative lupus glomerulonephritis. In both treatment arms, azathioprine (AZA) was used as long-term immunosuppressive therapy. The results of the trial indicate no significantly difference of remission and flare of the disease in patients taking a low-dose IVCY regimen and in those taking a high-dose regimen. Severe infectious side effects were less common in the low-dose group. The findings, therefore, call into question the current practice, based on the NIH trials, of treating all LN patients with an extended course of IVCY.<sup>(30)</sup>

#### **Mycophenolate mofetil as an alternative treatment**

An alternative treatment to severe LN is to use new immunosuppressive agents. Since infection

and gonadal toxicity are major concerns of CY used in the patients in their reproductive age, more effective, but less toxic, regimens are needed. Mycophenolate mofetil (MMF) is a new immunosuppressive agent that selectively inhibits activated lymphocytes and renal mesangial cells.<sup>(31)</sup> Experience with MMF in solid-organ transplantation has shown the safety of the drug and its superiority over AZA in the prevention of acute graft rejection. Data from experimental models of immune-mediated glomerulonephritis, particularly LN, have shown that MMF ameliorates autoimmune phenomena, retards renal damage, and improves the outcome.<sup>(32)</sup> Controlled studies have shown that MMF is as effective as CY in the induction of renal remission in the short term.<sup>(33)</sup> With the current dosage used in SLE, MMF appears to be well tolerated, with no serious toxicity reported. Significantly less ovarian toxicity compared with CY is particularly attractive for the consideration of MMF in LN.<sup>(33)</sup> However, the lack of long-term efficacy data and comparative studies with standard CY regimens is a major impediment for the

first-line use of MMF in high-risk patients at this moment.<sup>(34)</sup>

Thus, CY remains the most effective therapy for the initial treatment of aggressive LN. Recent studies continue to provide evidence of the efficacy of several dosing regimens, including daily oral administration<sup>(35)</sup> and intermittent low-dose<sup>(29)</sup> and high-dose IVCY. Interestingly, another recent protocol involving ultra-highdose (immunoablative) IVCY<sup>(36)</sup> has been reported. The results of ongoing and future prospective trials will be necessary to determine conclusively which CY regimen has the highest therapeutic index. Since CY is not optimally effective in all patients, and because no treatment program is completely nontoxic, future trials of other agents merit further testing against the best available regimen of CY.

### Maintenance treatment

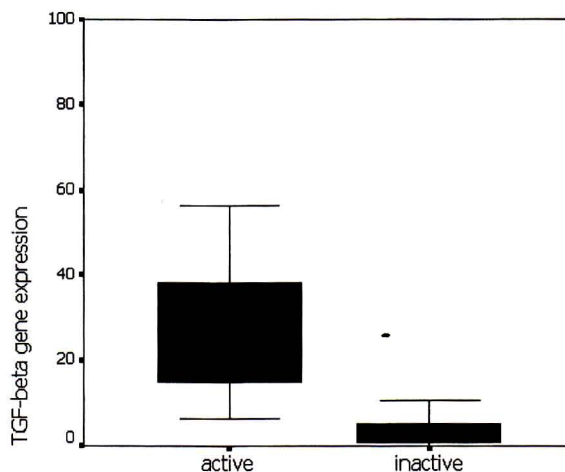
One of the most perplexing aspects of natural history of LN is its remitting and relapsing course. Modern treatment neither cures lupus nor completely prevents its exacerbations. Approximately one-third to one-half of the patients have a relapse of nephritis after achieving partial or complete remission of proliferative nephritis.<sup>(37)</sup> Several studies have shown that CY, AZA or even MMF are more effective than steroid alone in preventing relapse.<sup>(2,5,22,36)</sup> However, the risk-benefit of prolonged treatment, particularly CY, remains controversial. At present, one can justifiably choose between these three options; quarterly pulse IVCY, AZA or MMF. Although long-term therapy with MMF appears to be more efficacious and safer than quarterly IVCY<sup>(39)</sup>, the expensive cost of MMF precludes its use in most of our patients.

### Relapse

The clinical course of LN commonly includes episodes of relapse and remission. The cumulative rate of relapse of LN is approximately 25 and 50 percent at 5 and 10 years, respectively.<sup>(38,40)</sup> The relapse was significantly associated with subsequent deterioration of renal function. Follow-up renal biopsy studies have shown that patients who experience multiple episodes of active nephritis are at risk for progression to ESRD because each major exacerbation of nephritis is likely to leave residual and cumulative irreversible parenchymal damage.<sup>(40)</sup>

Considering the potential consequences of relapse, it is clearly important to recognize the earliest manifestation of these events and to respond accordingly. Unfortunately, none of the clinical or laboratory tools can precisely predict the nephritic flare. Determination of cellular casts or increased proteinuria may be useful. Serological markers such as C3 or C4 complement components, and anti-dsDNA levels are usually associated with the disease's activities. At present, intensify monitoring of urinary findings and serological activity is therefore recommended.<sup>(41)</sup>

Recent advancements in molecular diagnostic technology provide new tools in the diagnosis and prognosis of the disease. The study of molecular signals from urinary cellular components is a logical approach to early diagnosis of relapse of nephritis.<sup>(42)</sup> We currently explore the role of urinary cytokines and growth factors in LN and found their association with renal pathology (submitted manuscript) (Figure 1). Furthermore, the urinary molecular signals were detected weeks before the clinical and pathological manifestation. It is not known



**Figure 1.** The urinary mRNA levels of transforming growth factor beta (TGF- $\beta$ ) significantly increase during active state of lupus nephritis.

whether the early treatment decision based on urinary molecular signals may alter the course of the disease. Novel monoclonal antibodies designed according to these urinary or tissue molecular signals may elucidate new therapeutic targets of LN.

### Newer therapeutic strategies

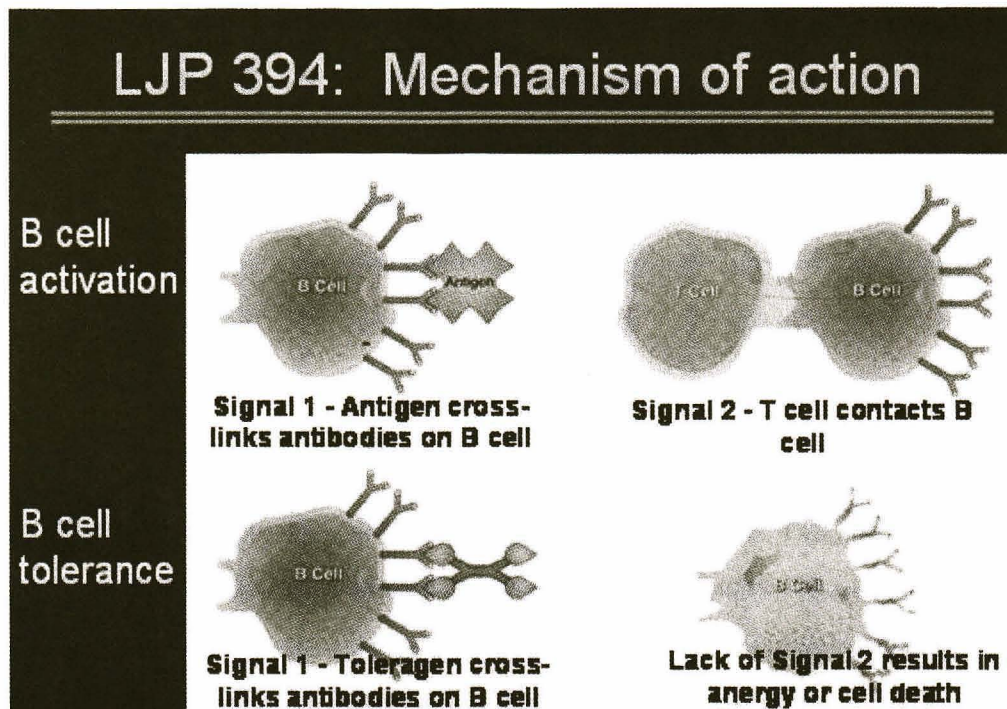
There are several reasons why we require new therapy for LN; 1) to control refractory disease since there remains 15-20 percent of patients who do not respond to standard regimens; 2) to avoid glomerular sclerosis and interstitial fibrosis due to repeated attacks of nephritis; 3) to prevent those flare of disease, and 4) to avoid side effects of current therapy particularly the gonadal toxicity.

Among the new strategies for immunosuppression in LN there are agents that act like CY and AZA which interfere with the synthesis of DNA and nucleotides, such as methotrexate, MMF, fludarabine and cladribine. Other strategies inhibitive effects of the activation signals for T cells (signals I and II by inhibition of calcineurin (cyclosporin and

tacrolimus) or interfere with the transduction signal that follows binding of IL-2 to the IL-2 receptor on activated T cells (mammalian target of rapamycin (mTOR) inhibitors, like sirolimus). Other strategies interfere with the effector phase of the immune response (monoclonal anti-bodies against cytokines or components of the complement system), interfere with molecules that are expressed on activated T cells (cytotoxic T lymphocyte (CTL)A-4, CD40 ligand (CD40L)), or aim at anergy of pathogenic B cells (abetimus or LJP-394) or at a reset of the immune system (autologous bone marrow transplantation).

To date, only a few new modalities have been sufficiently investigated to be regarded as promising. Among these are, in particular, MMF and LJP394. Here we will discuss only the agents tested in human LN which are LJP394 and CD40L mAb.

**LJP 394 (La Jolla Pharmaceutical 394 or abetimus sodium)** was designed to arrest the renal disease of SLE and to prevent renal flares by selectively reducing antibodies to dsDNA and their parent B cells via



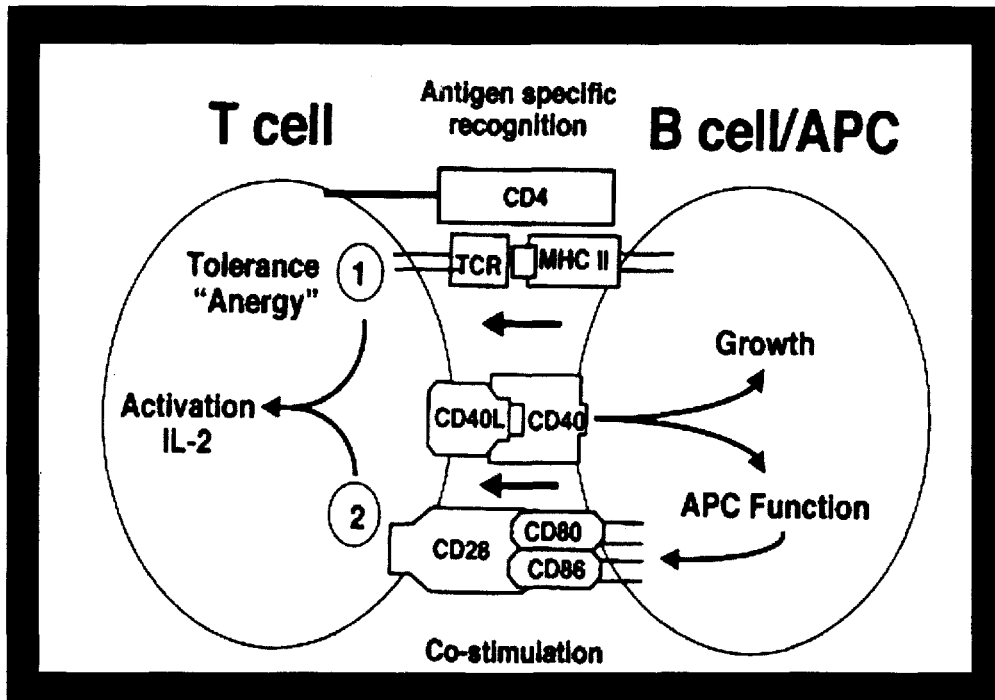
**Figure 2.** The mechanism of action of LJP 394: the crosslinking of membrane immunoglobulin on the surface of naive B cells can tolerize B cells via anergy or apoptosis.

antigen-specific tolerance. It consists of four 20-mers dsDNA epitopes conjugated to a pharmacologically inert triethylene glycol platform. LJP 394 is capable of crosslinking anti-dsDNA antibodies in solution or on the surface of B cells. Previous studies have shown that the cross-linking of membrane immunoglobulin on the surface of naive B cells in the absence of T cell help can tolerize B cells via anergy or apoptosis.<sup>(43)</sup> A prospective randomized controlled study on SLE patients with history of nephritis shows that LJP394 can prolong the time to relapse, decrease the number of attack and doses of steroid and CY.<sup>(44)</sup>

### Anti-CD40 Ligand Monoclonal Antibodies

CD40 is present on B cells, antigen presenting cells and endothelial cells. It interacts with CD40-ligand (CD40L, also known as gp39 or CD154)

that is upregulated on active CD4+ T-helper cells (but is also present on mast cells, basophils and activated platelets). The interaction between CD40 and its ligand results in proliferation and differentiation of B cells and is necessary for (auto) anti-body and cytokine production.<sup>(45)</sup> (Figure 3) The blockade of the CD40-CD40L pathway is supposed to reduce the production of T-cell-mediated antibody. Results of the treatment of SLE patients with anti-CD40L monoclonal antibodies have been very disappointing. In two phase-1 trials in patients with active SLE, monoclonal antibodies showed no effect and a trial with another product (that is successful in patients with refractory idiopathic thrombocytopenic purpura) was stopped because of severe thromboembolic complications were observed in treated SLE patients.<sup>(46)</sup>



**Figure 3.** CD40-CD40L pathway or second signal: Both TCR-MHC class II (first signal) and CD40-CD40L interactions (second signal) are required for T-cell and B-cell proliferation and differentiation. Blockade of second signal can down-regulate T-cell and B-cell responses. TCR=T-cell receptor. MHC=major histocompatibility complex.

## Conclusion

In order to provide optimal therapy for patients with LN, the high-risk group should have their pathology confirmed with renal biopsy. Approximately, 50 percent of patients who are biopsied, a proliferative lesion will be seen (WHO Type III or IV) and these patients should be considered for treatment with a combination of corticosteroids and immunosuppressive therapy. Patients with LN type I, II and V lesions usually receive corticosteroids and/or adjunctive therapy only.

Several options are available today for the treatment of diffuse proliferative LN. In the short term, excellent results can be obtained independently of the therapeutic approach chosen, provided that initial treatment is sufficiently vigorous. Unfortunately, there is a price to pay for every therapy, and this may particularly high in the long term. Corticosteroids alone

generally require high doses of use, leading to the well-known disfiguring, disabling, and life-threatening side-effects. Prolonged use of immunosuppressive agents, given either intravenously or orally, may result in ovarian failure, bone marrow toxicity, bladder toxicity, alopecia, infections, and cancer. A flexible strategy based on short-term aggressive treatment of flares, low-dose maintenance, and withdrawal of treatment when possible, allowed us to reduce severe iatrogenic morbidity while protecting kidney and other organs from the deleterious effects of SLE in most patients.

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## กิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์

ท่านสามารถได้รับการรับรองอย่างเป็นทางการสำหรับกิจกรรมการศึกษาต่อเนื่องสำหรับแพทย์ กลุ่มที่ 3 ประเภทที่ 23 (ศึกษาด้วยตนเอง) โดยศูนย์การศึกษาต่อเนื่องของแพทย์ จุฬาลงกรณ์มหาวิทยาลัย ตามเกณฑ์ของศูนย์การศึกษาต่อเนื่องของแพทย์แห่งแพทยสภา (ศนพ.) จากการอ่านบทความเรื่อง "ความรู้ใหม่เกี่ยวกับภาวะไตอักเสบจากโรคภูมิคุ้มกันบกพร่อง" โดยตอบคำถามข้างล่างนี้ ที่ท่านคิดว่าถูกต้อง โดยใช้แบบฟอร์มคำตอบท้ายคำถาม โดยสามารถตรวจจำนวนเครดิตได้จาก <http://www.ccme.or.th>

### คำถาม - คำตอบ

1. Which one of the following has a role in the pathogenesis of SLE ?
  - A. Genetics
  - B. Autoreactive lymphocyte
  - C. Cytokine
  - D. Complement
  - E. All of the above
2. Which one is INCORRECT regarding lupus nephritis ?
  - A. Expression of T-cells and MHC class II in the kidney of LN supports the role of T-cell in the development of the disease.
  - B. Kidney biopsy is helpful in diagnosis, treatment and prognosis of the disease.
  - C. The most common renal pathology is class IV WHO classification.
  - D. SLE patient can have silent form of LN.
  - E. Renal pathology is usually not altered.
3. Which one is INCORRECT regarding the treatment of diffuse proliferative LN ?
  - A. There are 2 phases of treatment; induction and maintenance phases.
  - B. Recommended immunosuppressive agents are cyclophosphamide plus steroids.
  - C. Intravenous cyclophosphamide has equal efficacy to treatment with steroids.
  - D. Mycophenolate is an alternative treatment.
  - E. LJP 394 is a new treatment that can prevent renal flare.

✍

คำตอบ สำหรับบทความเรื่อง "ความรู้ใหม่เกี่ยวกับภาวะไตอักเสบจากโรคภูมิคุ้มกันบกพร่อง"

จุฬาลงกรณ์เวชสาร ปีที่ 48 ฉบับที่ 6 เดือนมิถุนายน พ.ศ. 2547

รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/0406-(1009)

ชื่อ - นามสกุลผู้ขอ CME credit ..... เลขที่ใบประกอบวิชาชีพเวชกรรม.....  
ที่อยู่.....

1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)

4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)

4. Which one is not recommended in the maintenance phase ?
- A. Cyclophosphamide
  - B. Azathioprine
  - C. Mycophenolate
  - D. Anti CD40L
  - E. LJP 394
5. Which one is INCORRECT regarding LJP394
- A. Can reduce anti-dsDNA levels
  - B. Induce B-cell tolerance
  - C. Reduce T-cell proliferation
  - D. Prevent disease flare
  - E. diminish the severity of disease flare

เฉลย สำหรับบทความ รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/0405-(1007)

1. ง 2. ข 3. ก 4. ข 5. ง

สำหรับบทความ รหัสสื่อการศึกษาต่อเนื่อง 3-23-201-9010/0405-(1008)

1. B 2. C 3. D 4. E 5. E

ท่านที่ประสงค์จะได้รับเครดิตการศึกษาต่อเนื่อง (CME credit)  
กรุณาส่งคำตอบพร้อมรายละเอียดของท่านตามแบบฟอร์มด้านหน้า

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