The New Prognosis of Systemic Lupus Erythematosus: Treatment-Free Remission and Decreased Mortality and Morbidity

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Systemic lupus erythematosus is a chronic autoimmune disease that may affect different organ systems and have a relapsing and remitting course. The broad spectrum of clinical and immunological expression of SLE has implications in predicting possible outcomes and determining adequate treatment.

In the past, SLE was considered a rare and often fatal disease. Fortunately, it can now be considered, albeit relatively common, an illness in which mild forms, prolonged remission periods and long survival may be the rule [1–3]. On the other hand, as more patients with SLE are living longer, they also suffer chronic disease-associated morbidity and/or disability that may herald further illness, hospitalization and death. Thus, the health care of SLE patients must include not only disease control and prevention of mortality but also prevention of morbidity resulting from the toxic effects of drugs used for often unnecessarily long periods. Control of acute inflammation with the most efficacious treatment should be paralleled with adequate prevention or management of co-morbidity, without curtailing efforts to reduce and eventually withdraw all treatment for lupus itself. Appropriate education of patients, as well as comprehensive psychological and social support should also be included in the management of SLE.

This review will address the survival rates, prognostic factors for mortality, causes of death, specific organ damage, ultimate health status, quality of life, and long-term disease remission in SLE patients.

Mortality in SLE

Survival rates

The first longitudinal study to estimate survival of SLE patients was conducted by Merrell and Shulman in the mid 1950s [4], when they reported a survival rate of 51% 4 years after diagnosis in 99 patients at the Johns Hopkins Hospital. Recent reports from Europe and North America have demonstrated that survival rates improved progressively over time, reaching up to 97% at 5 years and close to 90% at 10 years [5–10]. The life expectancy of patients with SLE at 5 years was found to be similar to that of the general population of Sweden [5]. In Mexican patients, cumulative survival rates since the first symptom of SLE were 96 and 92% at 5 and 10 years, respectively [8]. These rates are similar to those reported by private practice centers in developed countries that care for considerable numbers of Hispanic patients [6]. However, studies from other developing countries reported 10 year survival rates ranging from 50 to 80% [11,12], although a Chilean study showed improved survival when compared to its own previous findings [12]. In contrast, a study from India suggests that survival of SLE patients has not improved in that country over the past decade [11]. The differences in survival of SLE patients over time between these two studies could be related to the economic conditions of their respective countries.

However, despite local differences, most prognostic studies have shown marked improvement in the survival of SLE patients over time, particularly in the last 10 years [2,3,5–10,12] [Table 1]. Indeed, mortality over a 24 year period decreased significantly more in SLE patients than in the general population matched for age and gender [2]. Nonetheless, the mortality in most SLE studies is still higher than in the general population [2,3].

Explanations for the improved survival of patients with SLE include earlier diagnosis, recognition of milder cases, and better therapy. Although no new therapies for SLE were introduced into general use in the last decade, the improved survival in SLE may have been influenced by better use of conventional therapy as well as advances in therapeutic approaches in general medical care — including better control of infections, hypertension and hyperlipidemia, and

Table 1. Survival rates in SLE patients from different American and European countries, 1991–1999

Country	City	Year	Survival rates (%)		Study (Ref.)
			5 yr	10 yr	
USA	Los Angeles	1991	97	93	Pistiner et al. [6]
USA	Stanford	1991	96	89	Seleznick et al. [7]
Mexico	Mexico City	1994	96	92	Drenkard et al. [8]
Chile	Santiago	1994	87	79	Massardo et al. [12]
Canada	Toronto	1995	93	85	Abu-Shakra et al. [9]
Europe	Multicenter	1999	95	–	Cervera et al. [10]

SLE = systemic lupus erythematosus

use of renal dialysis and transplantation [2,3]. Differences in patterns of treatment over time were observed in the Rochester study, with increased use of antimalarials and lesser use of cyclophosphamide and corticosteroids in 1980–1992 compared to1950–1979 [3]. Although this finding could be attributed to less severe disease in patients who were more recently diagnosed, it is more likely to reflect changing patterns of practice.

Major prognostic factors for mortality

• Social and demographic factors

Factors such as age at onset, gender, race and socioeconomic status are implicated in the prognosis of patients with SLE. Their contribution as predictors of mortality, however, is controversial and its interpretation difficult. It may depend on several variables, such as criteria selected for inclusion of patients, definitions, medical facilities, time and type of follow-up, and interrelationships between sociodemographic factors.

Age at onset. The course and prognosis of childhood lupus has traditionally been considered less favorable than that of adults. Renal and skin disease, fever, lymphadenopathy, vasculitis, seizures and serological abnormalities, as well as high levels of anti-DNA antibodies and low levels of complement, seem to be more frequent in younger SLE patients [6,13]. Older patients more commonly have interstitial lung disease, Sjogren's syndrome, musculoskeletal manifestations, serositis and myocarditis [13].

Although survival of pediatric lupus patients has been found to be shorter than that of older patients, especially when nephritis is present, the prognosis of lupus in childhood has also improved considerably in the last few years [14]. Actually, some researchers have found no relation between age at onset and survival in SLE [7] and others have even shown that older SLE patients have decreased survival [15]. Patients with disease onset before age 20 or after 50 could have a poorer outcome than those whose disease initiates between age 20 and 50. Younger patients tend to die more frequently from infection and lupus activity, whereas older patients die from cardiovascular complications and neoplasms [15].

Race and socioeconomic status. Most studies that have investigated differences between black and white SLE patients in the United States have shown that black patients have a poorer outcome, indicating a prognostic role of ethnic factors in SLE [15]. However, black patients also frequently have lower socioeconomic status, which has also been associated with poor prognosis in SLE and other chronic diseases [16]. Indeed, poverty may be an important determining factor in the prognosis of SLE patients in Hispanic communities in the United States or developing countries. This has not been sufficiently studied, but it is known that low income and scant education are associated with difficulties in access to health care, in ability to understand and recognize SLE symptoms, in the capacity to carry out medical recommendations, and in deficient social support, nutrition and employment opportunities [16]. Thus, black and Hispanic SLE patients from Los Angeles who had attained high socioeconomic status were found to have a prognosis similar to that of Caucasian whites [6]. A multicenter study in the U.S. showed that privately insured SLE patients had better survival at 1, 5 and 10 years (92%, 85% and 71%, respectively) than publicly insured patients, in whom survival was 86%, 68% and 53%, respectively [17]. One recent study of lupus populations in Alabama and Texas, with equivalent proportions of Caucasians, African Americans and Hispanics, found that genetic, ethnic and socioeconomic factors were associated both with organ disease presentation and with lupus activity [18]. Hispanic patients with the lowest socioeconomic status (43% of them being below poverty line) also had more cardiac and renal manifestations at the onset of lupus, and reached higher disease activity [18].

Gender. The influence of gender on survival of patients with SLE is controversial. Some studies did not show important differences in spectrum and disease severity or survival [15,17] between males and females. Others found that survival in males tends to be lower [6]. A joint study in 107 male SLE patients from Mexico and Colombia found them to have increased frequency of nephropathy and vascular thromboses, as well as higher levels of anti-DNA antibodies and corticosteroid requirement than did 1,209 female SLE patients [19]. SLE-related death, particularly due to nephritis, was also more frequent in male patients [19].

• SLE-related factors

Renal involvement. Multiple studies have shown that nephropathy is one of the most important factors determining decreased survival in SLE [6,8,10,12,17]. The strongest clinical indicators of mortality in patients with lupus nephropathy are increased serum creatinine at onset, hypertension, and the degree of proteinuria [12,17]. Survival analyses, according to kidney biopsies, have shown that proliferative and chronic lesions as well as a high score for renal disease activity index were associated with poor prognosis [12, 20].

Central nervous disease. Neuropsychiatric lupus includes a wide spectrum of neurological symptoms, some directly related to active lupus, others associated with antiphospholipid antibodies, and yet others reflecting infections, hypertension and metabolic complications or drug-related problems. CNS involvement was considered a poor prognostic factor in the past [17]. However, other studies found no influence of these manifestations on the survival of patients with SLE [21]. When stratified into focal and diffuse neurological involvement, only the focal factors, including stroke, seizure, transverse myelitis, myopathy and neuropathy, adversely influenced the long-term prognosis of SLE [21].

Antiphospholipid syndrome. Several individual manifestations related to antiphospholipid antibodies, such as thrombocytopenia, arterial occlusions, venous thrombosis and hemolytic anemia, were found to be linked to decreased

survival in a cohort of 667 Mexican patients with SLE [8]. This was also observed in SLE patients with antiphospholipid syndrome. Other authors also found a relationship between thrombocytopenia [12,15], thromboembolism [12] and a poor prognosis in SLE patients.

Disease activity and vasculitis. Patients with high lupus activity have increased risk for mortality, as shown in reports that included diverse disease activity indices [12]. The association of vasculitis as a manifestation of disease activity with increased mortality in Latin American SLE patients has recently been recognized [12,22], particularly when of visceral location [22].

Causes of death in SLE

Improved survival has also brought a change in the causes of death in SLE patients. Earlier studies noted that most patients died in the first years of the disease due to severe disease manifestations (e.g., nephritis, diffuse vasculitis and central nervous system disease). Other patients died from infections, frequently also associated with active disease. Infection remains an important cause of death throughout the course of illness. Recent studies from developed countries have emphasized a bimodal pattern of death in SLE, where deaths occurring within 5 years of diagnosis are more frequently due to active disease [9]. A second mortality peak occurs at around 13 years after diagnosis and is due to cardiovascular complications and end-organ failure not related to active lupus [9]. The prevalence of cardiovascular phenomena as causes of death in SLE has increased from 0% in the pre-steroid era to 15–25% in recent studies [6,9]. A multicenter European study noted that thromboses associated with antiphospholipid antibodies was another predominant cause of death in 12 of 45 patients who died at 5 years of follow-up [10].

Morbidity and disability

Morbidity and disability caused by a chronic disease such as SLE may result from acute or persistent severe disease activity, which produces specific organ damage directly related to the disease or as a consequence of its therapy. Frequently, morbidity is aggravated by low socioeconomic status and inadequate psychosocial support [23].

Specific organ damage

Long-term complications resulting either from SLE or as a consequence of its therapy may cause chronic damage in several organs or systems. Chronic manifestations directly related to SLE or to a secondary antiphospholipid syndrome that may yield a high morbidity include: cognitive impairment, cardiovascular and cerebrovascular disease, pulmonary hypertension, shrinking lung, renal failure, discoid skin lesions, and Jaccoud-like arthropathy.

- **Damage index**

Recently a damage index to estimate morbidity in SLE was developed and validated [24]. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR damage index) was created to estimate irreversible damage, regardless of cause, in 12 organ systems related to SLE, its treatment or intercurrent illness [24]. When applied to the Hopkins Lupus Cohort, it revealed that irreversible damage had occurred in the musculoskeletal system in 25% of patients, at the neuropsychiatric level in 15%, in the eyes in 13% and in the kidneys in 12% [25]. Avascular necrosis of bone, osteoporotic fractures and cataracts, the most common forms of damage found in that study, were linked to corticosteroid therapy rather than to SLE itself [25].

- **Cognitive dysfunction**

Neurocognitive deficits — evaluated by psychometric testing and characterized by impaired attention, memory, language and psychomotor speed — are more frequent in SLE patients than in controls, appearing even in patients without overt CNS manifestations and independent of disease activity. The course is frequently fluctuating, and is possibly associated over time with persistent anticardiolipin antibodies [26]. Studies designed to estimate both the pre-morbid level of functioning in patients with cognitive dysfunction and the impact of cognitive dysfunction on social, educational and occupational functioning are still needed.

- **Cardiovascular and cerebrovascular diseases**

Cardiovascular disease has been recognized as a major cause of morbidity in SLE patients. The cumulative incidence of angina or myocardial infarction in a young cohort of SLE patients from Baltimore was as high as 8%, with 53% having three or more risk factors to develop coronary artery disease [27]. The best predictors of coronary artery disease in SLE patients were age, the length of time on prednisone treatment, hypertension, hypercholesterolemia and obesity. A recent study found sustained hypercholesterolemia in 40% of patients with SLE tested within 3 years of diagnosis [28]. It was associated with older age at onset, increased cumulative dose of steroids, and no antimalarial therapy. Risk of hospitalization for acute myocardial infarction, congestive heart failure or cerebrovascular accident is increased in young women with SLE as compared to young women without SLE. All this information points to the importance of preventive measures to reduce modifiable risk factors for cardiovascular and cerebrovascular diseases in the management of SLE patients.

- **End-stage renal disease**

End-stage renal disease may develop in 5–26% of patients with lupus nephritis [29,30]. Normal initial serum creatinine levels or resolution of renal functional abnormalities within one year were observed to correlate with a lower risk of renal failure in these patients [29]. Hypertension and smoking are important and potentially modifiable factors that influence the prognosis of patients with lupus nephritis. Diffuse proliferative glomerulonephritis, high activity and chronicity indices, and the presence of tubulo-interstitial nephritis are biopsy findings that predict end-stage renal disease [30]. On the other hand, there seems to be a

tendency toward decreased clinical and serological activity after end-stage renal disease ensues. SLE patients are good candidates for dialysis and renal transplantation, having similar graft survival to that of non-SLE patients. Disease activity and recurrence of lupus nephritis are rare after transplantation [30]. A recent study found a higher risk of allograft loss in SLE patients than in non-SLE controls [31]. The presence of antiphospholipid syndrome and a history of having smoked may associate with decreased survival of transplanted kidneys [31].

• Infections

Infections have a high impact on the survival and morbidity of SLE patients. It is known that activity of SLE and impairment of the immune response relate to the increased risk of infection [32]. Pryor et al. [33] observed a higher prevalence of infection in patients treated with cyclophosphamide (45%) than in those on high dose corticosteroids (12%). The route of administration of cyclophosphamide (oral vs. intravenous) did not influence the prevalence of infection. Risk factors for infection vary for different agents, e.g., common bacterial organism or opportunistic infections. The latter are more frequent in patients with multi-organ disease than in those with any single organ manifestation, and correlate with higher corticosteroid dose, the use of cytotoxic drugs, and lower white blood cells at the nadir [33]. The incidence of infections in SLE patients treated with prednisone increases when doses are higher than 20 mg/day and administered for longer than 4 weeks. Patients treated with low doses of corticosteroids, however, are not spared the risk of infections. Thus, immunosuppressors and corticosteroids should be used as moderately, as infrequently, and as briefly as possible.

Disability, health status and quality of life

SLE has a high impact both on the physical state of patients and on their psychological and social lives. The recent interest among researchers in measuring the perception that SLE patients have about their health status and non-medical aspects of their lives has prompted the use of several questionnaires. Some of these instruments, whether arthritis-specific or generic, were designed to determine physical, psychological and social disability, and have recently been introduced and recommended for use as outcome measures to be used in clinical trials in SLE [34].

• Health status and quality of lfe

When compared to healthy controls, SLE patients have a poor perception of their general health, feeling affected in their physical function, vitality, social functioning, and mental health. They also have increased complaints of bodily pain and fatigue [35]. Some of the items included in health status instruments, in which SLE patients showed poor performances, were associated with higher disease activity, higher cumulative organ damage, lower social support, and less patient satisfaction with health care [35]. In addition, lower self-efficacy in disease management, lesser social support, and younger age at diagnosis are associated with higher disease activity. Ward et al. [23] observed that physical disability was related to depression, SLE disease activity to less social support, and cumulative organ damage to lower self-esteem and time orientation favoring the present over the future.

In a recent study from Israel comparing the quality of life of SLE patients with that of healthy controls [36], SLE patients were found to be more dissatisfied with their health, job, life satisfaction, active recreation, and independence. There was no association between quality of life scores and disease activity index, but lower scores of quality of life were found in patients with SLE and fibromyalgia as compared to SLE patients without fibromyalgia. These findings support the notion that specific psychosocial and physical interventions should be added to conventional drug therapy in order to obtain an optimal management of patients. Better control of fibromyalgia may also contribute to improving the quality of life in SLE.

• Fatigue

Chronic fatigue is a debilitating symptom that limits daily life activities and has a negative impact on the health status of SLE patients. Disease activity or fibromyalgia are considered as the main primary causes of fatigue in SLE. More recently, sleep disruption and, to a lesser degree, depression, have been considered the main direct mediators of fatigue in SLE patients [37]. On the other hand, another study found that a primary sleep disorder characterized by abnormalities in respiration and movement was common in SLE patients and related to restlessness and poor sleep at night [38]. This resulted in daytime sleepiness and fatigue. In addition, close to 40% of SLE patients have symptoms of depression, which can increase their fatigue and disability associated with other disease manifestations, decrease their physical activity, and interfere with their adherence to treatment. These findings suggest that, in addition to drug therapy, effective strategies for alleviating fatigue may include interventions for the detection and treatment of sleep pathologies and depressive symptoms.

Sustained remission

A few studies have described the clinical course of SLE, most of them stressing alternating periods of disease activity in one or more systems with periods of remission. Although long periods of treatment-free remission in patients with SLE were reported decades ago, somehow the notion that this could be achieved became lost until our observation that 156 of 667 Mexican patients underwent remission at least once during a mean follow-up of 11.6 years [1].

Remission was defined as at least one continuous year during which lack of clinical disease activity permitted withdrawal of all treatment for lupus proper. The duration of quiescent disease without therapy for SLE surely implies a previous much longer period without symptoms while drugs were being progressively withdrawn. According to our definition, we found 2.8 new cases of remission per 100

patients per year of follow-up. Treatment-free remission averaged almost 6 years in the 156 patients, representing half the time of total follow-up of the entire group. In some of the patients remission lasted up to 18 years, and most of them continue to be in remission almost 10 years later. Sixty-two of the 156 patients underwent remission within 2 years of the first clinical manifestation attributable to SLE, advocating the notion, also observed by others, that many SLE patients have active disease in the initial period followed by long remission periods. The mean length of time from SLE onset to the first remission was of 7.5 years in our 156 patients, with a range of 0.5–31.7 years. Thus, although the remission that occurred in most patients preceded the first 8 years of disease, some of them may need longer. According to a recent study from Spain [39], SLE patients with higher initial SLEDAI do achieve remission, although it may take longer to achieve than in those with lower initial disease activity indices. Gladman and coworkers [40] described SLE patients with low C3 determinations and/or high DNA uptakes despite having quiescent disease. However, most of our patients in clinical remission also had negative serological tests most of the time [1].

In our patients, 75 of the 156 who underwent remission had a subsequent relapse. Most of them, however, remitted again, and by the end of follow-up 73% of patients were still in remission. Although there were relapses after as many as 14 years of remission which, due to continued close observation, were promptly treated, the probability of undergoing remission increased with disease duration, reaching 70% of patients at 30 years. Remission was achieved in patients with mild disease as well as in those with severe initial renal, CNS or hematological disease. This was also stressed by Formiga et al. [39], who found no differences in the major initial clinical manifestations nor in the treatment of patients who achieved remission and those who did not.

Other studies have observed prolonged remissions in both adults and children with severe SLE who received different therapies. Interestingly, in a case-control study involving our same cohort we found that early occurrence of inflammatory myopathy was a strong predictor of subsequent remission. This could not be attributed to inclusion of patients with mixed connective tissue disease within our lupus cohort since we took great care to avoid it.

In our study, 2 of the 156 patients who achieved remission and 48 of the 511 who did not died during follow-up [1]. The two survival curves differed significantly. The better survival of patients who achieved remission occurred independently of the effect of disease manifestations (such as nephropathy and thrombocytopenia), which were found to cause increased mortality in our cohort [8].

Conclusions

Most SLE patients are now living longer and leading better lives than in the past. Survival is increasing faster in SLE patients than in the general population. The recognition and consequent reduction of factors leading to morbidity are important issues in clinical lupus research, and appropriate disease control with minimal treatment must always be sought. Aggressive, toxic and frequently unnecessary treatments in patients with relatively little disease activity may result in organ damage and should be avoided.

In most SLE patients, lupus disease activity tends to decrease with time, permitting their management with less toxic therapy such as antimalarials, or low doses of corticosteroids. A significant number of patients may become, at times indefinitely, symptom-free and require no medication. We hope that physicians will heed the notion that medication can be stopped in SLE patients; they should avoid continuing indefinitely, out of groundless fear, with small doses of prednisone despite complete clinical remission. Until a cure for lupus is found, achievement of treatment-free remission must be considered the current goal in managing lupus patients. Its attainment renders a positive impact on the overall health status of SLE patients, not only by reducing the toxic effects of drugs but also by improving their quality of life in the psychological and social spheres.

References

1. Drenkard C, Villa AR, García-Padilla C, Pérez-Vázquez ME, Alarcón-Segovia D. Remission of systemic lupus erythematosus. *Medicine* 1996;75:88–98.
2. Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT. Mortality studies in systemic lupus erythematosus. Results from a single center. III: Improved survival over 24 years. *J Rheumatol* 1997;24:1061–5.
3. Uramoto KM, Mitchet CJ, Thumboo J, Sunku J, O'Fallon WM, Gabriel SE. Trends in the incidence and mortality of systemic lupus erythematosus, 1950–1992. *Arthritis Rheum* 1999;42:46–50.
4. Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. *J Chronic Dis* 1955;1:12–32.
5. Jonsson H, Nived O, Sturfelt G. Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine* 1989;68:141–9.
6. Pistiner M, Wallace DJ, Nessim S, Metzger AL, Klinemberg JR. Lupus erythematosus in the 1980s: a survey of 570 patients. *Semin Arthritis Rheum* 1991;21:55–64.
7. Seleznick MJ, Fries JF. Variables associated with decreased survival in systemic lupus erythematosus. *Semin Arthritis Rheum* 1991;21:73–80.
8. Drenkard C, Villa AR, Alarcón-Segovia D, Pérez-Vázquez ME. Influence of the antiphospholipid syndrome in the survival of patients with systemic lupus erythematosus. *J Rheumatol* 1994;21:1067–72.
9. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. I: Causes of death. *J Rheumatol* 1995;22:1259–64.
10. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Paz Lavilla A, Aydintug O, Jedryka-Goral A, De Ramón E, Fernández-Nebro E, Galeazzi M, Haga H-J, Mathieu A, Houssiau F, Ruiz-Irastorza G, Ingelmo M, Hughes GRV, and the European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1000 patients. *Medicine* 1999;78:167–75.
11. Kumar A, Malaviya AN, Singh RR, Singh YN, Adya CM, Kakkar R. Survival in patients with systemic lupus erythematosus in India. *Rheumatol Int* 1992;12:107–9.
12. Massardo L, Martínez ME, Jacobelli S, Villarroel L, Rosenberg H, Rivero S. Survival of Chilean patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 1994;24:1–11.

13. Hashimoto H, Tsuda H, Hirano T, Takasaki Y, Matsumoto T, Hirose S. Differences in clinical and immunological findings of systemic lupus erythematosus related to age. *J Rheumatol* 1987;14:497–501.
14. Abeles M, Urman JD, Weinstein A, Lowenstein M, Rothfield NF. Systemic lupus erythematosus in the younger patient: survival studies. *J Rheumatol* 1980;7:515–22.
15. Reveille JD, Bartolucci A, Alarcón G. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. *Arthritis Rheum* 1990;33:37–48.
16. Liang MH, Partridge AJ, Daltroy LH, Straaton KV, Galper SR, Holman HR. Strategies for reducing excess morbidity and mortality in blacks with systemic lupus erythematosus [Review]. *Arthritis Rheum* 1991;34:1187–96.
17. Ginzler EM, Diamond HS, Weiner M, Schlesinger M, Fries JF, Wasner C, Medsger TA, Ziegler G, Klippel JH, Hadler NM, Albert DA, Hess EV, Spencer-Green G, Grayzel A, Worth D, Hajn BH, Barnett EV. A multicenter study of outcome in systemic lupus erythematosus. I: Entry variables as predictors of prognosis. *Arthritis Rheum* 1982;25:601–11.
18. Reveille JD, Moulds JM, Ahn C, Friedman AW, Baethge B, Roseman J, Straaton KV, Alarcón GS, for the LUMINA Study Group. Systemic lupus erythematosus in three ethnic groups. I: The effects of HLA class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. *Arthritis Rheum* 1998;41:1161–72.
19. Molina JF, Drenkard C, Molina J, Cardiel MH, Uribe O, Anaya JM, Gomez LJ, Felipe O, Ramirez LA, Alarcón-Segovia D. Systemic lupus erythematosus in males. A study of 107 Latin American patients. *Medicine* 1996;75:124–30.
20. McLaughlin J, Gladman D, Urowitz MB, Bombardier C, Farewel VT, Cole E. Kidney biopsy in systemic lupus erythematosus. II: Survival analysis according to biopsy results. *Arthritis Rheum* 1991;34:1268–73.
21. Kovacs JA, Urowitz MB, Gladman DD. Dilemmas in neuropsychiatric lupus [Review]. *Rheum Dis Clin North Am* 1993;19:795–814.
22. Drenkard C, Villa AR, Reyes E, Abello M, Alarcón-Segovia D. Vasculitis in systemic lupus erythematosus. *Lupus* 1997;6:235–42.
23. Ward MM, Lotstein DS, Bush TM, Lambert E, Vollenhoven R, Neuwelt CM. Psychosocial correlates of morbidity in women with systemic lupus erythematosus. *J Rheumatol* 1999;26:2153–8.
24. Gladman DD, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. *Arthritis Rheum* 1996;39:363–9.
25. Petri M, Barr SG, Zonana-Nach A, Madger L. Measures of disease activity, damage, and health status. The Hopkins Lupus Cohort Experience. *J Rheumatol* 1999;26:502–3.
26. Menon S, Jameson-Shortall E, Newman SP, Hall-Craggs MR, Chinn R, Isenberg DA. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. *Arthritis Rheum* 1999;42:735–41.
27. Petri M, Spence D, Bone L, Hochberg MC. Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine* 1992;71:291–302.
28. Bruce IN, Urowitz MB, Gladman DD, Hallet DC. Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol* 1999;26:2137–43.
29. Levey AS, Shu-Ping L, Corwin HL, Kasinath BS, Lachin J, Neilson EG, Hunsicker LG, Lewis EJ and The Lupus Nephritis Collaborative Study Group. Progression and remission of renal disease in the Lupus Nephritis Collaborative Study. Results of treatment with prednisone and short-term oral cyclophosphamide. *Ann Intern Med* 1992;116:114–23.
30. Berden JHM. Lupus nephritis [Review]. *Kidney Int* 1997;52:538–58.
31. Stone JH, Amend WJC, Criswell LA. Outcome of renal transplantation in ninety-seven cyclosporine-era patients with systemic lupus erythematosus and matched controls. *Arthritis Rheum* 1998;41:1438–45.
32. Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus [Review]. *Semin Arthritis Rheum* 1996;25:318–36.
33. Pryor BD, Bologna SG, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:1475–82.
34. Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P. Outcome measures to be used in clinical trials in systemic lupus erythematosus. *J Rheumatol* 1999;26:490–7.
35. Sutcliffe N, Clarke AE, Levinton C, Frost C, Gordon C. Isenberg DA. Associates of health status in patients with systemic lupus erythematosus. *J Rheumatol* 1999;26:2352–6.
36. Abu-Shakra M, Mader R, Langevitz P, Friger M, Shlomi C, Neumann L, Buskila D. Quality of life in systemic lupus erythematosus: a controlled study. *J Rheumatol* 1999;26:306–9.
37. McKinley PS, Quellette SC, Winkel GH. The contributions of disease activity, sleep patterns, and depression to fatigue in systemic lupus erythematosus. *Arthritis Rheum* 1995;38:826–34.
38. Valencia-Flores M, Resendiz M, Casta o VA, Santiago V, Campos RM, Sandino S, Valencia X, Alcocer J, Garcia-Ramos G, Bliwise R. Objective and subjective sleep disturbances in patients with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:2189–93.
39. Formiga F, Moga Y, Pac M, Mitjavila F, Rivera A, Pujol R. High disease activity at baseline does not prevent a remission in patients with systemic lupus erythematosus. *Rheumatology* 1999;38:724–7.
40. Gladman DD, Urowitz MB, Keystone EC. Serologically active clinically quiescent systemic lupus erythematosus. A discordance between clinical and serologic features. *Am J Med* 1979;66:210–15.

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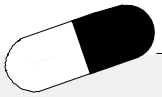
Capsule



Internalization of peptide-MHC complexes by T cells

Peptide-major histocompatibility complex protein complexes (pMHCs) on antigen-presenting cells (APCs) are central to T cell activation. Huang et al. report that within minutes of peptide-specific T cells interacting with APCs, pMHCS on APCs formed clusters at the site of T cell contact. Thereafter, these clusters were acquired by T cells and internalized through T cell receptor-mediated endocytosis. During this process, T cells became sensitive to peptide-specific lysis by neighboring T cells (fratricide). This form of immunoregulation could explain the "exhaustion" of T cell responses that are induced by high viral loads and may serve to down-regulate immune responses.

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