

Analysis of Complete Remission in Lupus Patients over a period of 32 years.

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BACKGROUND: Systemic Lupus Erythematosus (SLE) is characterized by an unpredictable and fluctuating course. Although various methods have been developed to measure disease activity, there is still a lack of consensus about the optimal criteria for SLE remission.

The principal aim of our study was to identify the number of lupus patients achieving a complete remission (implying that for 3 years there were no clinical or serological features and no treatment with steroids and immunosuppressive drugs) in a single cohort of patients followed for a period of up to 32 years. In addition, we have identified patients in clinical but not serological remission (known as serologically active, clinically quiescent disease (SACQ)) and vice versa. We were particularly interested to determine the factors associated with complete remission.

METHODS: Eligible patients were followed up in the University College Hospital Lupus cohort from January 1978 until December 2010 for a period of at least 3 years. Complete remission was defined as a period of at least 3 years with clinical inactivity (BILAG scores of C, D or E only) and laboratory remission (no antibodies to dsDNA and normal complement C3 levels) and being off-treatment with corticosteroids and immunosuppressants. Antimalarials and nonsteroidal anti-inflammatory were allowed.

RESULTS: Of 624 lupus patients at our hospital, a total of 532 patients met the strict inclusion criteria for the study. Of these 532 patients, 77 patients (14.5%) achieved complete remission for at least 3 years, 23 (4.3%) achieved complete remission for a minimum period of 10 years. Ten of these 77 patients were subsequently lost to follow up, and interestingly flares occurred subsequently in 15 of the 67 remaining patients (22.4%). Three patients relapsed after the tenth year of remission. Forty-five (8.5%) patients fulfilled the requirement for SACQ, and sixty-six (12.4%) patients achieved only serological remission.

CONCLUSIONS: Our study indicated that 14.5% of lupus patients achieved a complete remission for three years. However, flares may continue to occur beyond ten years of remission. Long term follow up of SLE is thus mandatory.

SIGNIFICANCE AND INNOVATION

Patients with SLE often develop the disease in their teenage years/early 20s. They are keen to get prognostic information. Most studies limit their outcome reporting to 5-10 year periods. In this study we describe the long-term follow-up over a period of 32 years focusing on a key question about whether patients who go into full clinical and serologic remission (for 3 years) will remain in remission subsequently. Our data extracted from our very long-term and careful follow-up indicates that 22.4% of patients will flare even after 3 years of remission. We believe these data are important and will help guide what rheumatologists say to their patients with lupus.

INTRODUCTION:

Systemic Lupus Erythematosus (SLE) is characterized by an unpredictable and fluctuating course with relapses and remissions over many years. However, the prognosis and survival of SLE patients have improved significantly in the last decade ¹.

Few reports describing long-term remission rates, in excess of fifteen years exist, and also there is inadequate knowledge about predictors of relapse.

Some patients may be clinically asymptomatic without steroids, but have persistently raised anti-dsDNA or anti-nucleosome antibodies also known as serologically active clinically quiescent (SACQ) ^{2,3}.

Various indices have been developed to measure disease activity e.g. the British Isles Lupus Assessment (BILAG), the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the European Community Lupus Activity Measure (ECLAM), and have been known to be reasonably equivalent ^{4,5}. However, there is still a lack of consensus about the optimal criteria to define SLE remission.

The aim of our study was to identify, in retrospect, the number of lupus patients achieving a complete remission (minimum of 3 years) in a single cohort of patients followed for periods of up to 32 years at University College Hospital. The time point chosen was arbitrary, but we felt as clinicians that any patient lacking clinical features of lupus for 3 years would, at least ostensibly, tend to encourage us to believe that the disease might truly have abated. In addition, we noted the frequency of patients that achieved clinical remission or prolonged serologically active clinically quiescent disease (SACQ), and those who only achieved serological remission. We also sought to determine disease characteristics associated with complete remission (no clinical or serological activity and on nothing more than Hydroxychlorquine).

MATERIALS AND METHODS:

PATIENTS

We enrolled patients fulfilling the revised ACR criteria for classification of SLE and the data we have recorded about them were retrospectively assessed ⁶.

Eligible patients were followed up principally at University College Hospital from January 1978 until December 2010 for a period of at least 3 years and were required to have made at least one visit per year.

DATA

The study variables included sex, ethnicity, age at the time of SLE onset, time of follow-up, duration of disease, time to achieve remission, duration of remission, existence of flare, the presence of mucocutaneous involvement (rash, alopecia, mucosal ulcers), musculoskeletal involvement, cardiopulmonary manifestations (serositis, shrinking lung syndrome, alveolar haemorrhage), central nervous system (CNS) disease (including psychosis, seizures, paresis or paralysis, and cranial nerve involvement), kidney involvement (nephritis documented invariably by biopsy), haematological manifestations (thrombocytopenia, Antiphospholipid syndrome), vasculitis (documented by biopsy), laboratory results (anti-double stranded DNA antibodies, complement C3) and medication.

MEASUREMENTS

Anti-dsDNA antibodies were considered to be positive if the patient had a ELISA level result (Shield Diagnostics, Dundee, UK) above the upper limit of normal (>50 IU) on at least two occasions.

Serum C3 levels were measured by laser nephelometry.

The method of measuring disease activity was the classic BILAG system, which is also sensitive to disease flares⁵.

OUTCOME MEASURES

The primary goal was to assess the complete remission rate in our lupus patients during a minimum period of three years. We also determined the frequency of patients that achieved serological remission only, and clinical remission (also known as SACQ). Other assessed outcomes were flares, death rate, and disease characteristics associated with complete remission

DEFINITIONS

Complete remission was defined as a minimum 3-year consecutive period of no disease activity, specifically patients who had a score of C, D or E on the BILAG index only, were off steroids and immunosuppressant drugs, except antimalarials which were permissible, had normal laboratory tests (no antibodies dsDNA and normal serum levels of C3 complement), and had not had a recurrence or any other reason for treatment failure before the time point of interest.

Clinical remission or SACQ was defined as a score of C, D or E on the BILAG index and absence of pharmacotherapy (corticosteroids and immunosuppressants save antimalarials) but remained an active serologic profile (low C3 complement level and/or high antidoublestranded DNA antibody levels) for at least 3 consecutive years.

Serological remission was characterized by normal complement C3 and anti-ds DNA antibody levels but with persistent clinical activity (score of A or B on the BILAG index, and/or treatment with steroids or immunosuppressive drugs) for at least 3 consecutive years.

Clinical Flare (or relapse) was defined by the development of score A or B on the BILAG index, with or without a low C3 complement serum level or positive Anti-dsDNA result.

Serological Flare (or relapse) required decreased level of C3 complement and/or a high Anti-dsDNA antibody result, in the group of patients who have achieved only serological remission but remained clinically active.

STATISTICAL ANALYSIS

We used the Statistical Package for the Social Sciences (SPSS) for all conventional analyses. The results were described as the median (maximum and minimum range). Continuous variables were analyzed (by univariate analysis) using nonparametric Kruskal-Wallis tests. Group data were compared by X^2 test. Only associations with P value <0.05 were considered statistically significant.

RESULTS

We excluded those who had been diagnosed before 1978 (37 patients) or after 2010 (8 patients), and those for whom we had insufficient data or irregular follow-up because some patients moved away either within the UK or overseas (47 patients). Of 624 lupus patients at our hospital, 532 patients were followed for a 3 year-period minimum and also required at least one visit per year (Table 1).

The number of patients who did not achieve clinical and serological remission was 344 (64.7%). Nine patients were taking DMARD's with or without steroids due to other underlying disease (3 for kidney transplant, 2 for psoriasis, 1 for bowel inflammatory disease, 1 for primary biliary cirrhosis, 1 for primary pulmonary hypertension and 1 for Lymphoma non-Hodgkin's).

Seventy-seven patients (14.5%) achieved complete remission as defined in the Methods for at least 3 years. Complete remission occurred a median time of 9 years after the time of being diagnosed (the minimum and maximum range of time since diagnosis was 0 – 27 years). The median time of remission was 7 years (the minimum and maximum range of time was 3 – 24 years), and interestingly 23 patients (4.3%) achieved complete remission for a minimum period of 10 years.

Of the 77 patients who had at least 3-year remission, 10 were lost to follow-up while still in remission. There was at least one flare in 15 of these 67 remaining patients (22.4%). Of these flares, 10 were simply clinical whereas 5 had alterations in laboratory and clinical features. Three patients relapsed after the tenth year of remission (at 12, 16 and 18 years).

Forty-five (8.5%) patients fulfilled the requirement for clinical remission (SACQ), though ten patients had a flare after 3-year time. One patient was lost follow-up after the sixth year of remission. (Figure 1).

In the group of 77 patients who had a complete remission, forty-eight (62.3%) were still on hydroxychloroquine and twenty-nine (37.7%) were off-treatment. Thus only 5.5% of our SLE patients cohort were in complete remission without any medication. In the group of 45 patients who achieved only clinical remission (SACQ), twenty-eight (62.2%) were still taking hydroxychloroquine and seventeen (37.8%) had withdrawal of therapy.

Sixty-six (12.4%) patients only achieved a serological remission, and 14 had serological relapses. All remained clinically active. Four patients were lost follow-up after achieving the third, fourth, fifth and sixth year of serological remission respectively.

We could not identify a trigger that caused relapses in 69% of our patients. A percentage of 15% of the patients relapsed immediately after pregnancy and 8% flared post-infections. We did not find any statistically significant association between the frequency of relapses and clinical manifestations such as renal, mucocutaneous, cardiopulmonary, musculoskeletal, neurological, hematological, vasculitis or the presence of overlap syndromes.

A comparison of the baseline characteristics and clinical parameters of the patients who achieved complete remission, clinical remission (SACQ), serological remission and absence of remission is shown in Table 2 and Table 3, respectively.

We could not determine, accurately, an association between the likelihood of remission and sex and ethnicity because of the small size sample. However, there is a higher frequency among non-Caucasian patients in the non-remission group.

Patients who went into complete remission were older at the time of diagnosis ($p < 0.001$) and had a longer disease duration ($p < 0.001$).

Seventy-one deaths of patients included in our study were reported and its main causes were infections (28.2%), cancer (23.9%) and atherosclerosis (12.7%). The median age at death was 45 years (range of age at death was 16 years – 88 years). In the complete remission group only four patients died whereas 61 deaths occurred in those who never achieved remission ($p < 0.001$).

Achieving remission is further negatively influenced by renal ($p < 0.001$), neurological ($p = 0.002$) and cardiopulmonary involvement ($p < 0.001$). Patients with major mucocutaneous involvement also have a lower likelihood of achieving remission ($p < 0.05$). No statistically significant difference was found in Sjogren's syndrome ($p = 0.230$).

DISCUSSION

We found that 14.5% ($n = 77$) of our lupus patients achieved a complete remission for three years. In addition, only 5.5% (29 patients) of our lupus cohort were in complete remission without any medication (including antimalarials). Previous studies have reported different values of incidence and prevalence among patients who achieve remission (which in most

publications means clinical remission) in their respective populations. The lack of consensus about the criteria for remission has influenced in these discordant results.

In 1964, Dubois and Tuffanelli described a high percentage of remission (35%) in a study of 520 patients during a period of follow-up to 13 years, without specifying the remission criteria they used. They also determined that nine patients had spontaneous remission that lasted at least 10 years of duration⁸.

Tozman et al.⁹ published one of the first prospective studies about complete remission in SLE patients, describing a proportion of 4/160 (2.5%) patients achieving complete remission and being off immunosuppressants for a median time of 75-months follow-up, in spite of a history of renal involvement.

Formiga et al.¹⁰ reported that 24 of 100 Caucasian patients achieved remission at least for a year and remained in remission for an average time of 55 months. They used the SLEDAI score to assess activity since the onset of disease, and found that higher SLEDAI scores correlated with later remission. However, even by those with severe disease could go into remission. Despite the fact that their percentage of patients in remission is bigger than ours, our study population has greater ethnic diversity, given that Caucasians have better prognosis. In addition, 17 of 24 (70%) remained in remission, similar to our findings in which 52 of our 77 lupus patients (68%) have remained in remission.

Drenkard et al.¹¹ determined that 156 of 667 (23.4%) patients achieved remission without any therapy (even antimalarials) for a minimum of one-year period, and almost half of these patients (12%) remained in remission for at least 5 years. Twenty-nine patients of our lupus cohort went into remission without any medication (including antimalarials) at least for 3 years. However, they did not use a conventional index to measure activity such as SLEDAI or BILAG, and they were not as strict about changes in laboratory results to classify patients into different types of remission. They found that 41/156 patients with renal involvement and 19/156 patients with neurological disease achieved clinical remission.

Another study identified thirteen (4%) of 305 patients with serological and clinical remission¹². Five of these patients remained in complete remission for a minimum period of 3 years. Nevertheless, their remission criteria were different from ours. They performed an ANA test instead of measuring levels of DNA binding, and also included asymptomatic patients who were taking a low dose of corticosteroids in the group of remission. Eight of these thirteen patients (2.6%) were not receiving treatment. They, like us, found a lower prevalence of kidney and central nervous system involvement in those going into remission. Unfortunately, we restricted our serological studies to dsDNA antibodies and serum levels of C3 complement, so we do not have available information on ANA.

In 2005, Urowitz et al.¹³ found that only 12 of 703 patients (1.7%) fulfilled criteria for prolonged complete remission (SLEDAI=0) after 5 years without therapy. Their research demonstrated as might be expected, that being less restrictive with respect to the remission criteria (permitting antimalarials as treatment), increases frequency of achieving remission.

We excluded from the patients in complete remission and SACQ those who had become asymptomatic, but who were still taking treatment, including a minimal dose of steroids, so no drug might contribute or affect the result. There is evidence which supports the use of antimalarials for the prevention of flares or recurrences^{14, 15}. Sixty-two percent of our patients who achieved remission were taking antimalarials.

Gladman et al. found 14 of 180 (7.8%) patients who were in clinical remission with persistent laboratory abnormalities (SACQ), were off all medication for 4 years². We determined that 45 of our lupus patients (8.5%) were in SACQ and 10 of them subsequently relapsed.

Further studies have shown that patients with a prolonged SACQ disease accumulate less damage supporting the idea of managing them with close monitoring without therapy during this period^{16, 17}.

Some studies based on the oncology literature chose five years for defining a period of remission¹³. Although arbitrary we felt that a 3-year period with no clinical or serological abnormalities and on no major therapy would be sufficient to convince most rheumatologist and SLE patients that a viable remission had been achieved. However, there is no agreement about time of remission. Encouragingly, we found that 23 patients (4.3%) achieved remission beyond 10 years.

Previous studies have used an SLEDAI score to evaluate disease activity^{10, 13}. However, in our study, disease activity was measured by BILAG. The BILAG index is a useful and reliable instrument to measure disease activity for each organ-based system¹⁸. Moreover, the BILAG index correlates highly with other methods of measuring activity such as SLEDAI, and BILAG can easily detect flares^{4, 7}.

Although it could be argued that by allowing our lupus patients with BILAG C scores to be included in what we have referred to as “clinical remission”, this group of patients might more accurately be referred to as low/no activity. In reality however, many BILAG C scores were achieved rather easily eg a very transient photosensitive induced rash or a clinical feature no longer regarded as reflecting disease activity eg the presence of Raynaud’s phenomenon or items which are in fact damage items eg a fixed livedo reticularis rash or a tendon contracture or an avascular necrosis. Indeed the ease with which a C score could be obtained in many of the organs or systems in the original BILAG activity index led the BILAG group to modify its index which is now known as BILAG-2004.¹⁹

Another limitation in the study is the challenge we faced to link different types of immunosuppression to the various types of remission. We have not found it possible to achieve this because many of the patients were taking multiple immunosuppressives either concomitantly or sequentially, some were treated with Rituximab and immunosuppression and about a third were co-managed at other hospitals to which we do not have ready access to patient notes.

Similar to previous studies, our findings confirmed that those who had an increased probability of complete remission were older at the time of diagnosis and had longer disease duration at study ^{11, 13}. Currently, we have very limited data about menopausal status of the female patients, so that although of interest, we cannot easily relate it to disease remission.

Our result agreed with those of Gladman et al.² with respect to the lower frequency of cutaneous, renal and neuropsychiatric involvement in patients achieving clinical remission. Heller et al. reported similar findings in 1985 ¹². In addition, we determined that achieving remission is negatively impacted by cardiopulmonary involvement.

One important association was that patients who did undergo remission were less likely to die than those who did not, highlighting the importance of achieving remission. It is known that the survival in those who do not achieve remission is impaired ¹¹.

Our study is limited in that we did not assess the cumulative dosage and length of immunosuppressive therapy and total corticosteroid use over the entire follow-up period.

There were 15 flares, and 3 of 77 of our SLE patients had relapses after 10 years of complete remission. We thus emphasize the importance of continued close monitoring because it is even almost impossible to predict disease progression. We did not however assess the frequency of patients who have relapsed and remitted again and the time that have passed till they suffered new flares.

Even though, we could not evaluate association between the probability of the several types of remission and sex and ethnicity because of the small size sample, we found a significant number of non-Caucasian patients in the group who did not achieve remission and those who achieved only serological remission. Nossent et al. ²⁰ and Rekha Lopez et al. ²¹ demonstrated poorer prognosis among Afro-Caribbean lupus patients with higher disease activity measures. White patients have a milder disease compared to those with African or Hispanic ethnicity ^{20, 21, 22}.

A large number of patients (n=92) did not meet the inclusion criteria because most of them moved abroad or had a premature unknown death or were attended other clinics in the UK. Additionally, those who were diagnosed after 2010 and before 1978 were excluded in order to avoid a bias because of the influence of an older and probably postmenopausal age. Moreover, patients who were diagnosed after 2010 had insufficient follow-up time to meet our criteria for remission.

Sadly, we did not assess the cumulative disease activity or cumulative damage during the follow-up. The aim of our study was to describe the characteristics of patients at baseline in order to determine if some of them could be used as a predictor of disease outcomes. The full range of factors or features of the patients that may influence in remission and recurrence have not yet been determined.

In conclusion we found that 14.5% of lupus patients achieved a complete remission after three years. Although harder to achieve in those patients with major organ involvement, it can occur. However, flares may continue happening beyond ten years of remission. Long term follow up of SLE is thus mandatory.

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Table 1. Baseline Parameters of lupus patients

Parameter		Value	Percentage / Statistical Dispersion
Sex	Female	489	91.9 %
	Male	43	8,1 %
Ethnicity	Caucasian	294	55.3 %
	Black/Afrocaribbean	106	10.9 %
	Asian	22	4.1 %
	Indian, Pakistan, Bangladesh	74	13.9%
	Other background	36	6.8%
Age at diagnosis (years)		27 (1- 27 years)	Median (range minimum and maximum)
Time of follow-up (years)		12 (1- 34 years)	Median (range minimum and maximum).
Disease duration at study (years)		14 (1- 37 years)	Median (range minimum and maximum).

Figure 1. Frequency of patients achieving different types of remission and no remission

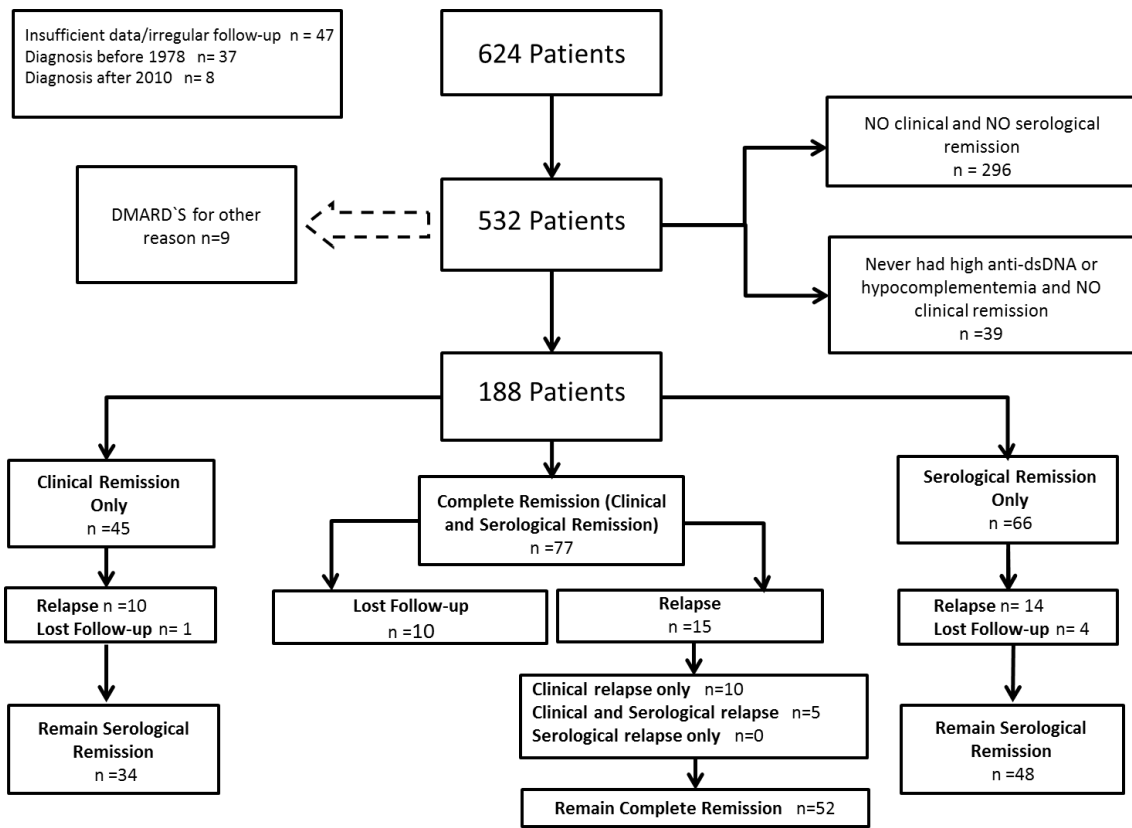


Table 2. Baseline characteristics according to different types of remission and no remission

Parameter		Complete Remission	Clinical remission (SACQ)	Only Serological remission	No Remission
Sex	Female n(%)	69 (14.1%)	44 (9%)	60 (12.3%)	316 (64.6%)
	Male n(%)	8 (18.6%)	1 (2.3%)	6 (14%)	28 (65.1%)
Ethnicity	Caucasian n(%)	56 (19%)	32 (10.9%)	31 (10.5%)	175 (59.5%)
	Black/Afrocaribbean n(%)	5 (4.7%)	7 (6.6%)	14 (13.2%)	80 (75.5%)
	Asian n (%)	1 (4.5%)	1 (4.5%)	1 (4.5%)	19 (86.4%)
	Indian, Pakistan, Bangladesh n (%)	10 (13.5%)	3 (4.1%)	15 (20.3%)	46 (62.2%)
	Other background n (%)	5 (13.9%)	2 (5.6%)	5 (13.9%)	24 (6.7%)
Age at diagnosis (years)		33 (13-74) (p< 0.001)	30 (10-74)	28 (12-62)	25 (1-77)
Disease duration at study (years)		18 (5-34) (p<0.001)	16 (4-36)	15.5 (4-34)	13 (1-37)
Years until remission		9 (0-27)	7 (0-32)	8 (0-31)	0
Time of remission (years)		7 (3-24)	5 (3-19)	5.5(3-23)	0
Frequency of death n(%)		4 (5.6%)	1 (1.4%)	5 (7%)	61 (86%) p<0.001

Median, maximum range and minimum ranges have been used to express the results of : Age at diagnosis, disease duration at study, years until remission and time of remission.

Table 3. Clinical Parameters of the patients who achieved different types of remission and no remission

Parameter	Complete Remission	Clinical remission (SACQ)	Only Serological remission	No Remission
Musculoskeletal involvement	75/77	43/45	64/66	316/344
Mucocutaneous involvement	70/77	43/45	64/66	290/344 (p=0.006)
Kidney involvement	8/77	9/45	24/66	134/344 (p<0.001)
Cardiopulmonary involvement	19/77	7/45	28/66	148/344 (p<0.001)
Digestive involvement	0/77	1/45	0	4/344
Haematological manifestations (Thrombocytopenia, Haemolytic anaemia)	4/77	1/45	3/66	30/344
Vasculitis	1/77	1/45	4/66	21/344
CNS involvement	4/77	1/45	15/66	55/344 (p=0,002)
Antiphospholipid Syndrome	4/77	5/45	7/66	32/344
Sjogren Syndrome	15/77	7/45	9/66	38/344
Overlap (RA, Myositis, Scleroderma)	3/77	2/45	9/66	35/344

RA: Rheumatoid Arthritis. CNS: Central Nervous System.