# Patterns of drug therapy in newly diagnosed Spanish patients with systemic lupus erythematosus

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## Abstract

### Objective

*This is the first Spanish multicentric inception lupus cohort, formed by SLE patients attending Spanish Internal Medicine Services since January 2009. We aimed to analyse drug therapy during the first year of follow-up according to disease severity.*

### Methods

*223 patients who had at least one year of follow-up were enrolled upon diagnosis of SLE. Therapy with prednisone, pulse methyl-prednisolone, hydroxychloroquine, immunosuppressives and calcium/vitamin D was analysed.*

### Results

*Prednisone was given to 65% patients, at a mean (SD) daily dose of 11 (10) mg/d. 38% patients received average doses >7.5 mg/d during the first year. Patients with nephritis and with a SLEDAI ≥6 were treated with higher doses of prednisone. 81% of patients were treated with hydroxychloroquine, with higher frequency among those with a SLEDAI ≥6 (88% vs. 68%, p<0.001). The use of immunosuppressive drugs and methyl-prednisolone pulses was higher in patients with a baseline SLEDAI ≥6, however, differences were no longer significant when patients with lupus nephritis were excluded. The use of calcium/vitamin D increased with the dose of prednisone, however, 43% of patients on medium-high doses of prednisone did not take any calcium or vitamin D.*

### Conclusion

*This study gives a real-world view of the current therapeutic approach to early lupus in Spain. The generalised use of hydroxychloroquine is well consolidated. There is still a tendency to use prednisone at medium to high doses. Pulse methyl-prednisolone and immunosuppressive drugs were used in more severe cases, but not as steroid sparing agents. Vitamin D use was suboptimal.*

**Key words**

systemic lupus erythematosus, therapy; glucocorticoids, hydroxychloroquine, immunosuppressive drugs, vitamin D, lupus nephritis, lupus activity, damage.

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## Introduction

Systemic lupus erythematosus (SLE) is a multisystemic disease with a wide range of clinical manifestations. Several drugs can be used to treat lupus, including antimalarials, glucocorticoids, immunosuppressive drugs and, more recently, biological agents, either licensed (belimumab) or off-label (rituximab). Patterns of drug administration are greatly dependent on the type and severity of organ involvement, but also on evolving recommendations and personal preferences.

The management of SLE should not be just directed to control disease manifestations. Recent guidelines of an international task force state that "treatment of SLE should aim at ensuring long-term survival, preventing organ damage, and optimising health-related quality-of-life, by controlling disease activity and minimising comorbidities and drug toxicity" (1). Moreover, a number of consensus documents recommend considering the universal use of hydroxychloroquine in lupus patients with no contraindications (1-3), limiting as much as possible the dose and time of treatment with glucocorticoids (1), treating severe forms of lupus nephritis with immunosuppressive drugs (2-4) and preventing glucocorticoid-dependent osteoporosis (5).

RELES (Registro Español de Lupus Eritematoso Sistémico) is a research project of the Spanish Group of Autoimmune Diseases (Grupo de Enfermedades Autoinmunes, GEAS) within the Spanish Society of Internal Medicine (Sociedad Española de Medicina Interna, SEMI). RELES is the first Spanish multicentric inception lupus cohort, in which patients with a new diagnosis of SLE have been included since January 2009. Thus, the analysis of patterns of initial therapy during the first year of follow-up can give a clue of the current trends of lupus treatment in Spain. More specifically, this study aimed to analyse the differential use of glucocorticoids, antimalarials and immunosuppressive drugs according to disease severity at presentation. As a secondary objective, measures to spare glucocorticoids and to prevent steroid toxicity were assessed.

## Patients and methods

*RELES inception cohort*

As of July 2014, 306 patients were enrolled in RELES. Among them, 223 patients had completed at least one year of follow-up after the diagnosis and constituted the study population. All patients were attended at Internal Medicine Services of 29 public Spanish Hospitals, 27 of them University Hospitals. Patients were enrolled at the time when at least 4 ACR classification criteria were met (6). Recruitment started in January 2009. Data were collected prospectively and entered into a central computerised database with an online access via an individual user name and password. All patients signed an informed consent document. The study protocol was approved by the Institutional Research Ethics Boards of the coordinating centre (Hospital Universitario Cruces) and of all participating centres, in accordance to the Helsinki declaration.

Demographic, laboratory, immunological and clinical variables were collected at diagnosis, with specific definitions for each variable available in the web-based database. For patients with a diagnosis of lupus nephritis, a histopathologial confirmation was urged, being accomplished in 85% of cases. Every modification of drug therapy was entered in the database, thus it was possible to calculate the exact cumulative dose of prednisone, i.v. methyl-prednisolone, hydroxychloroquine and immunosuppressive drugs for a given period of time. Prednisone therapy was rendered particularly important based on its great potential for toxicity. For the purposes of this study, the cumulative dose at the first month and first year was transformed into the average daily dose, expressed in mg/d; this was further recoded into four categories, according to Butgereit *et al*. (7): no prednisone, low dose (up to 7.5 mg/d), medium dose (up to 30 mg/d) and high dose (over 30 mg/d). The Registry Coordinating Center contacted individually the investigators in order to assure the validity and the completion of data, with special focus on treatment variables.

*Statistical analysis*

Descriptive data were generated, using

percentages, means and standard deviations (SD). Such data included demographic characteristics, clinical manifestations at diagnosis, immunological profile, baseline Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) (8) and drug therapy received within the first year of follow-up.
In order to analyse the relation between lupus therapy and disease severity, the prescription of prednisone, *i.v.* methyl-prednisolone, hydroxychloroquine and immunosuppressive drugs (cyclophosphamide, azathioprine, mycophenolate sodium or mofetil and methotrexate) was compared using Chi-square test, Fisher's exact test, non-paired Student's t-test or univariate lineal regression, as appropriate, in patients with and without nephritis and in patients with a baseline SLEDAI ≥6 and <6, with and without nephritis. The use of calcium and vitamin D according to prednisone dose was also analysed.
All the statistical calculations were made with STATA 11.2 (STATA Corp, TX, USA).

## Results

One hundred and ninety-nine patients were women (89%), and 193 (86%) were Caucasian. The mean (SD) age at diagnosis was 43 (15) years. The clinical manifestations and immunological profiles of the cohort are summarised in Table I.
The mean (SD) SLEDAI score at diagnosis was 9.8 (7.8). Six patients (3%) had a SLEDAI score of zero, 65 patients (30%) had an SLEDAI score <6 and the remaining 152 patients (68%) had a baseline SLEDAI ≥6. Sixty patients (30%) had an SLEDAI >12.

### *Therapy during the first year (Table II)*

Prednisone was part of the initial therapy in 110 (49%) patients. During the first month of follow-up, the mean (SD) daily dose of prednisone-treated patients was 26 (22) mg/d. Twenty-four (11%) patients received low doses, 46 (21%) medium doses and 40 (18%) high doses. Within the first year, the number of patients given prednisone increased (144 patients, 65%), however, the mean (SD) average daily dose of prednisone-treated patients decreased to 11 (10) mg/d. Sixty-one (27%) received low doses, 77 (35%) medium doses and only 6 (3%) high doses.
Hydroxychloroquine was given to 182 patients (81%) within the first year. Eighty-eight patients (39%) received one or more immunosuppressive drug: 26 (12%) cyclophosphamide, 32 (14%) azathioprine, 20 (9%) methotrexate, 42 (19%) mycophenolate (sodium or mofetil) and 1 (0.5%) tacrolimus. 15 patients (7%) did not receive any therapy with prednisone, hydroxychloroquine or immunosuppressive drugs. The different drug combinations are shown on table 2. Thirty-four patients (15%) received methyl-prednisolone bolus within the first year. One hundred and one patients (45%) were given calcium and/or vitamin D: 84 (38%) calcium, 95 (42%) vitamin D and 78 (35%) both.

### *Therapy, disease severity and organ involvement (Table III)*

Patients with nephritis were more likely to be treated with immunosuppressive drugs than patients without renal disease (40/47, 85%, *vs.* 46/176, 26%; $p<0.001$). Regarding individual drugs, patients with lupus nephritis received more often cyclophosphamide and mycophenolate, whilst no difference was found for azathioprine, and they were also given pulse methyl-prednisolone more often (45% *vs.* 7%, $p<0.001$). They also received higher doses of prednisone: the mean (SD) daily dose during the first year was 14 (12) mg/d *vs.* 5.4 (8) mg/d in patients without nephritis ($p<0.001$). Likewise, 34/47 (72%) patients with nephritis received medium-high average daily doses of prednisone during the first year, compared with 47/176 (26%) of those with no nephritis ($p<0.001$). On the other hand, the proportion of patients treated with hydroxychloroquine was similar in those with and without nephritis (78% *vs.* 80%, $p=0.8$).
Differences were more marked among the 35 patients with biopsy-proven class III, IV or V lupus nephritis. Of note, 33/35 (94%) patients in this group received immunosuppressive drugs (mainly cyclophosphamide, 49%, and/or mycophenolate, 80%) *vs.* 55/188 (29%) in the remaining patients ($p<0.001$). On the other hand, hydroxychloroquine was used in a high proportion of patients whether they had class III, IV or V lupus nephritis (29/35, 83%) or not (153/188, 81%, $p=0.8$).
The baseline SLEDAI was associated with the average daily prednisone dose at one year (r-square 0.12, $p<0.001$).

**Table I.** Baseline clinical manifestations and immunological profile in the 223 patients of the RELES cohort.

| | n (%) |
|---|---|
| Malar rash | 55 (25%) |
| Discoid rash | 17 (8%) |
| Subacute cutaneous lupus | 29 (13%) |
| Livedo reticularis | 20 (9%) |
| Alopecia | 32 (14%) |
| Raynaud | 43 (19%) |
| Cutaneous vasculitis | 8 (4%) |
| Photosensivity | 98 (44%) |
| Oral ulcers | 64 (29%) |
| Arthralgias | 169 (76%) |
| Arthritis | 98 (44%) |
| Seizures | 2 (1%) |
| Psychosis | 1 (0.5%) |
| Myelitis | 1 (0.5%) |
| Neuropathy | 3 (1.5%) |
| Intracranial hypertension | 2 (1%) |
| Lupus nephritis | 47 (21%) |
| Class I | 2 (1%) |
| Class II | 3 (1.5%) |
| Class III | 5 (2%) |
| Class IV | 24 (11%) |
| Class V | 6 (3%) |
| No biopsy | 7 (4%) |
| Pleuritis | 28 (13%) |
| Pericarditis | 25 (11%) |
| Haemolytic anaemia | 19 (9%) |
| Lymphopenia | 123 (55%) |
| Leukopenia | 77 (35%) |
| Thrombocytopenia | 32 (14%) |
| Deep venous thrombosis | 17 (8%) |
| Pulmonary thromboembolism | 5 (2%) |
| Stroke | 5 (2%) |
| ANA | 220 (99%) |
| Anti-DNA | 138 (62%) |
| Anti-Ro | 93 (42%) |
| Anti-La | 39 (18%) |
| Anti-Sm | 46 (21%) |
| Anti-$U_1$RNP | 44 (20%) |
| Lupus anticoagulant | 49 (22%) |
| Anticardiolipin antibodies IgG (medium-high titer) | 34 (15%) |
| Anticardiolipin antibodies IgM (medium-high titer) | 16 (7%) |
| Anti$_2$-β2 glycoprotein I IgG | 26 (11%) |
| Anti-β2$_2$ glycoprotein I IgM | 27 (12%) |
| Low C3 | 118 (53%) |
| Low C4 | 105 (47%) |

ANA: antinuclear antibodies; HCQ: hydroxychloroquine; SD: standard deviation.
*during the first year after SLE diagnosis.

**Table II.** Drug therapy during the first year of follow-up.

| Drug | n (%) |
|---|---|
| Prednisone (1st month) | 110 (65%) |
| Prednisone (1st month) mean (SD) dose | 26 (22) mg/d |
| Prednisone (1st month) average daily dose | |
| Low dose (≤7.5 mg/d) | 24 (11%) |
| Medium dose (>7.5-30 mg/d) | 46 (21%) |
| High dose (>30 mg/d) | 40 (18%) |
| Prednisone (1st year) | 144 (65%) |
| Prednisone (1st year) mean (SD) dose | 11 (10) mg/d |
| Prednisone (1st year) average daily dose | |
| Low dose (≤7.5 mg/d) | 61 (27%) |
| Medium dose (>7.5-30 mg/d) | 77 (35%) |
| High dose (>30 mg/d) | 6 (3%) |
| HCQ (1st year) | 182 (81%) |
| Pulse methyl-prednisolone (1st year) | 34 (15%) |
| Any immunosuppressive drug (1st year) | 88 (39%) |
| Cyclophosphamide (1st year) | 26 (12%) |
| Azathioprine (1st year) | 32 (14%) |
| Methotrexate (1st year) | 20 (9%) |
| Mycophenolate (sodium or mofetil) (1st year) | 42 (19%) |
| Tacrolimus (1st year) | 1 (0.5%) |
| Drug combinations (1st year): | |
| HCQ only | 54 (24%) |
| Prednisone only | 12 (5%) |
| Prednisone + HCQ | 54 (24%) |
| Prednisone + immunosuppressives | 11 (5%) |
| HCQ + immunosuppressives | 7 (3%) |
| Prednisone + HCQ + immunosuppressives | 67 (30%) |
| Calcium and/or vitamin D (1st year) | 101 (45%) |

**Table III.** Treatment according to lupus severity.

| | Nephritis (n=47) | No nephritis (n=176) | *p* |
|---|---|---|---|
| Average prednisone dose | | | |
| Mean (SD) | 14 (12) mg/d | 5.4 (8) mg/d | <0.001 |
| Medium/high doses of prednisone | 34 (72%) | 41 (26%) | <0.001 |
| Pulse methyl-prednisolone | 21 (45%) | 12 (7%) | <0.001 |
| Immunosuppressives | 40 (85%) | 46 (26%) | <0.001 |
| Hydroxychloroquine | 37 (78%) | 141 (80%) | 0.8 |
| | SLEDAI ≥6 (n=152) | SLEDAI <6 (n=71) | *p* |
| Average prednisone dose Mean (SD) | 8.8 (10.3) mg/d | 3.7 (7.8) mg/d | 0.0002 |
| Medium/high doses of prednisone | 73 (48%) | 10 (14%) | <0.001 |
| Pulse methyl-prednisolone | 29 (19%) | 5 (7%) | 0.02 |
| Immunosuppressives | 71 (47%) | 17 (24%) | 0.001 |
| Hydroxychloroquine | 134 (88%) | 48 (68%) | <0.001 |
| | SLEDAI ≥6, no nephritis (n=107) | SLEDAI <6, no nephritis (n=69) | *p* |
| Average prednisone dose Mean (SD) | 6.5 (8) mg/d | 3.6 (8) mg/d | 0.02 |
| Medium/high doses of prednisone | 39 (36%) | 9 (13%) | 0.001 |
| Pulse methyl-prednisolone | 7 (6%) | 5 (7%) | 0.9 |
| Immunosuppressives | 31 (29%) | 16 (23%) | 0.4 |
| Hydroxychloroquine | 96 (90%) | 48 (70%) | 0.006. |

SD: standard deviation.

Accordingly, patients with a baseline SLEDAI ≥6 were treated with higher average doses of prednisone: 8.8 (10.3) mg/d *vs*. 3.7 (7.8) mg/d, $p$=0.0002. Patients with a baseline SLEDAI ≥6 received medium-high doses of prednisone more frequently than patients with SLEDAI <6 (73/152, 48% *vs*. 10/71, 14%; $p$<0.001). More patients in this group were treated with immunosuppressive drugs (71/152, 47% *vs*. 17/71, 24%; $p$=0.001). Regarding individual drugs, only cyclophosphamide (24/152, 16% *vs*. 2/71, 3%; $p$=0.005) and mycophenolate (38/152, 25%, *vs*. 4/71, 6%; $p$=0.001) were used more frequently by patients with a baseline SLEDAI ≥6. The combination prednisone-hydoxychloroquine-immunosuppressives was used much more frequently among patients with a baseline SLEDAI ≥6 (57/152, 37% *vs*. 10/71, 14%, $p$<0.001).

After excluding patients with nephritis from this analysis, differences in the use of immunosuppressive drugs were no longer significant (Table III). On the other hand, patients without nephritis with a baseline SLEDAI ≥6 were still more likely to be given medium-high daily doses of prednisone than those with a SLEDAI <6 (39/107, 36% *vs*. 9/69, 13%; $p$=0.001). Only a minority of patients without nephritis were given pulse methyl-prednisolone, irrespective of baseline SLEDAI score (7/107, 6% *vs*. 5/69, 7%; $p$=0.9). It was noteworthy that patients with a baseline SLEDAI ≥6 received hydroxychloroquine more frequently than those with lower scores (134/152, 88% *vs*. 48/71, 68%; $p$<0.001). This was also true for patients without nephritis (96/107, 90%, *vs*. 48/69, 70%; $p$=0.006).

*Prednisone, calcium and vitamin D*

Among the 144 patients treated with prednisone within the first year, 82 (57%) received therapy with calcium and/or vitamin D, *vs*. 19/79 (24%) patients not taking prednisone ($p$<0.001). The use of calcium and/or vitamin D increased with the average daily dose of prednisone: 35/61 (57%) of those with low doses, 43/77 (56%) of those with medium doses and 4/6 (67%) of those with high doses ($p$<0.001). However, 36/83 (43%) of patients on medium-high doses of prednisone did not take any calcium or vitamin D during the first year of follow-up.

## Discussion

This study offers a unique view of therapy trends in recently diagnosed Spanish lupus patients. Detailed data regarding therapy are difficult to obtain

**Table IV.** Initial therapy in observational lupus cohorts.

| Study/year (ref) | number of patients | Period of treatment | Baseline SLEDAI | Oral glucocortoids (%) | Prednisone average dose | Pulse methyl-prednisolone (%) | Antimalarials (%) | Immuno-suppressives (%) |
|---|---|---|---|---|---|---|---|---|
| Alarcon/1999 (9) | 229 | Enrolment | 10.8* | 89% | 19 mg/d | NA | 56% | CYC 16%<br>AZA 8% |
| Urowitz 2008 (10) | 389 | Enrolment | 9.6 | 63% | NA | NA | 46% | 31% |
| Nossent/2010 (11) | 200 | 1 year after diagnosis | 12.2 | 83% | 8.7 mg/d | 33% | 46% | CYC 24.5%<br>AZA 25%<br>Other 10.5% |
| Parker/2014 (12) | 1150 | Enrolment | 5.4 | 69% | 20 mg/d | 4.9% | 66% | 40% |
| RELES/2015 | 223 | 1 year after diagnosis | 9.8 | 65% | 11 mg/d | 15% | 81% | 39%<br>CYC 12%<br>AZA 14%<br>MTX 9%<br>MF 19%<br>TACRO 0.5% |

*SLAM score. CYC: cyclophosphamide; AZA: azathioprine; MTX: methotrexate; MF: mycophenolate (mofetil or sodium); TACRO: tacrolimus.

from inception cohorts (Table IV), thus it is not easy to compare specific indications in real-life settings.

Similar to other cohorts, RELES patients showed high SLE activity level at enrollment (Table I). Sixty-five percent of patients received prednisone during the first year of follow-up. The mean daily dose given to patients treated with prednisone was 11 mg/d, lower than in most other cohorts (Table IV) and with a substantial reduction compared with the amount given during the first month; however, as many as 38% of patients were treated with average medium-high doses of prednisone (*i.e.* >7.5 mg/d) during the first year.

As shown in Table IV, the use of such medium-high doses is actually the rule during in the early phases of lupus (9, 11, 12). Sixty-four percent of patients treated with steroids in the Hopkins Cohort received average doses of prednisone over 10 mg/d during the first 5 years of disease, compared with 26% between 11 and 15 years (13). A recent study by the German Collaborative Arthritis Centres has not found a relevant reduction in the proportion of patients treated at enrolment with prednisone doses >7.5 mg/d over the time, with figures around 25% of patients in both subcohorts 1994-1998 (n=467) and 2004-2008 (n=376) (14).

However, common does not necessarily mean good. Glucocorticoids are nowadays recognised as one of the main causes of damage in SLE (15). Cataracts, osteoporotic fractures, osteonecrosis, coronary artery disease and stroke have all been associated with either the cumulative dose or the use of high doses of prednisone (13). Thus, strategies to reduce medium-long term doses of prednisone since the early phases of SLE should be implemented. Recent treat-to-target recommendations by an international task force state that "lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible, glucocorticoids should be withdrawn completely" (1). Although no specific guidelines define the lowest acceptable dose of prednisone, only doses ≤5 mg/d can be considered as reasonably safe according to published evidence (16, 17).

One of the means to reduce the dose of glucocorticoids is adding antimalarials to the long-term treatment. Indeed, antimalarials have shown a significant reduction in damage accrual and mortality in lupus patients (18). Although the use of hydroxychloroquine is now recommended for most patients with SLE (1), including those with lupus nephritis (2-4), it is still difficult to find cohort studies with more than 50% of patients receiving hydroxychloroquine (Table IV). Unfortunately, they are still preferentially prescribed to patients with mild disease and usually withdrawn in the event of serious organ involvement (11). By contrast, hydroxychloroquine was used by most patients of the RELES cohort, and, remarkably, patients with and without nephritis received the drug in a similar proportion around 80%; such percentage increased to 88% of patients presenting with a baseline SLEDAI ≥6, compared with only 68% with an SLEDAI <6, 21% of whom did not receive any treatment at all.

The association of immunosuppressive drugs can be used with and steroid-sparing aim. This effect has been well documented for methotrexate (19). However, they are not usually prescribed with such indication, either in our cohort or in those represented in Table IV. Whenever the prescription of immunosuppressive drugs has been analysed, it has been actually associated with high doses of oral glucocorticoids, being preferentially given to patients with lupus nephritis. Immunosuppressives use in RELES was low in patients without nephritis, even among those with high SLEDAI at presentation.

Methyl-prednisolone pulses have consistently shown a lack of association with glucocorticoid-related damage (13, 16), being a more potent and rapid way of using glucocorticoids to treat inflammation (7). Accordingly, methyl-prednisolone pulses have been proposed for inducing remission in severe SLE cases (20), with proven efficacy in patients with lupus nephritis (21-23).

When used in the setting of multi-drug regimes including hydroxychloroquine and immunosuppressive drugs or rituximab, they have allowed a marked reduction in the dose of oral prednisone without a resulting decrease in efficacy (22, 23), even in patients with highly active SLE at presentation without severe renal involvement (24). It is noteworthy that patients in the study by Nossent *et al*. (11) received the highest number of pulse therapy and the lowest dose of oral prednisone (Table IV). Alike immunosuppressive drugs, the use of methyl-prednisolone therapy in RELES was largely limited to patients with nephritis.

Finally, specific recommendations have been published regarding the prevention of osteoporosis, one of the most devastating effects of glucocorticoids (5). Unfortunately, the use of calcium and vitamin D was clearly suboptimal in our cohort.

This study has a number of limitations. The multicentric design, with the participation of almost 30 centres, adds heterogeneity to the clinical profile of patients and to the specific indications of therapy. All the participants belonged, by definition, to Internal Medicine Departments, who look after patients with SLE and other autoimmune diseases in many Spanish hospitals. A recent study of the RELESSER group, from the Spanish Society of Rheumatology, did not include data on the initial therapy after the diagnosis (25). Thus, whether patients attending Spanish Rheumatology Departments receive similar therapeutic schemes is a matter of further investigation.

In summary, this first report of the RELES cohort gives a real-world view of the contemporary therapeutic approach to early lupus in Spain. While current recommendations concerning the generalised use of hydroxychloroquine irrespective of the severity of disease are well accomplished, there is still a tendency to the use of prednisone at medium to high doses, with a suboptimal use of both steroid-sparing strategies (mainly pulse methyl-prednisolone and immunosuppressive drugs outside lupus nephritis) and steroid-related osteoporosis prevention guidelines.

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