Differences between rheumatologists and other internists regarding diagnosis and treatment of systemic lupus erythematosus

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Abstract

Objectives. To compare the diagnostics and treatment of SLE patients in the care of rheumatologists with patients in the care of other specialties within a geographically complete cohort.

Methods. Nine different sources were used to identify SLE patients resident in Oslo between 1999 and 2008. Only SLE patients fulfilling four or more of the updated 1997 ACR criteria were included. Data were extracted from medical records. The patients were classified into three groups according to each patient’s responsible doctor’s specialty.

Results. A total of 325 SLE patients were included in the study. Of these, 227 had solely been in the care of rheumatologists (rheumatology group), 34 had solely been in the care of nephrologists, hematologists or infectious disease specialists (non-rheumatology group) and 64 had been in the care of both rheumatologists and other specialists (multidisciplinary group). Even though patients in the non-rheumatology group and multidisciplinary group showed similar disease characteristics, patients in the non-rheumatology group were less often tested for aPLs (68% vs 94%; \( P = 0.001 \)) and less often treated with HCQ (12% vs 78%; \( P < 0.001 \)).

Conclusions. In contrast to rheumatologists, non-rheumatologists do not routinely test all SLE patients for aPLs, and rarely prescribe HCQ. These findings indicate that more communication between different specialists caring for SLE is needed, and highlights an area in need of agreement.

Key words: systemic lupus erythematosus, physician’s practice patterns, prescription pattern, hydroxychloroquine, anti-phospholipid antibody.

Introduction

SLE is a heterogeneous disease with a wide range of clinical manifestations and severity. Thus, SLE patients are likely to be treated with a variety of medical specialties depending on the symptoms and the organs affected. Patients with predominant musculoskeletal complaints will most likely be referred to a rheumatologist, while patients presenting with GN or nephrotic syndrome are most often admitted to a department of nephrology. A SLE patient exhibiting cutaneous manifestations would preferably be referred to a dermatologist. SLE patients with initial manifestations such as thrombocytopenia or haemolysis are frequently seen by haematologists. It is therefore likely that the clinical pattern reported differs according to which specialized care centre is presenting the SLE cohort. This aspect of SLE has been rarely addressed. Similarly, the difference in prescription patterns among rheumatologists and other specialists has been infrequently addressed [1, 2]. The aim of this study was to identify all SLE patients in our region and determine whether there were any differences regarding diagnostic procedures and preferences of therapy between rheumatologists as opposed to other internist subspecialities.

Patients and methods

Study area

Oslo is the capital and the largest city in Norway, with a population of 580,000, of whom 20% are immigrants of non-European origin. The health-care system in Norway...
is almost fully state funded. At the time of the study, there were six hospitals in Oslo. All six hospitals have an internal medicine service and two hospitals have a rheumatology service. Since 2004, the rheumatology service of all SLE patients has been sectioned to the Rheumatology Department at Oslo University Hospital, Rikshospitalet. In Norway, most specialists in internal medicine and rheumatology are hospital based, and at the time of the study, there were one nephrologist and two rheumatologists in private practice in Oslo.

Identifying patients with SLE
The sources for identifying patients were inpatient and outpatient hospital discharge databases for the adult patient population (≥16 years) in the six hospitals in Oslo containing the 10th revision of the World Health Organization International Classification of Diseases (ICD-10) diagnosis code for every patient visit from 1 January 1999 to 30 December 2008, the Connective Tissue registry at Oslo University Hospital, Rikshospitalet and the SLE cohort from Diakonhjemmet Hospital established in 1995 [3]. Additionally, the rheumatologists in private practice were asked to send data for their SLE patients. Only patients living in Oslo in the period from 1999 to 2008 and fulfilling four or more of the updated 1997 ACR [4] classification criteria were included in the study. The study was approved by the Regional Committee for Medical Research Ethics and the National Data Inspectorate.

For the purpose of comparing treatment, diagnostic procedures and monitoring of rheumatologist vs non-rheumatologist, the patients were divided in three groups. The rheumatology group included patients solely followed and treated by rheumatologists. However, some of these patients were seen by a neurologist or other internist for a specific medical problem, but with no change in SLE treatment. The non-rheumatology group included patients followed and treated exclusively by internists other than rheumatologists, and the multidisciplinary group included patients followed and treated by both rheumatologists and other internist specialties.

Data collected
The information collected from medical records included demographic data, the time of onset of the first SLE symptom, ACR criteria defined according to the guidelines [4], APS according to the Sapporo criteria [5], onset of nephritis, nephrotic proteinuria, reduced renal function (estimated glomerular filtration rate of <60 ml/min per 1.73 m² or creatinine >100 μmol/l for men and >90 μmol/l for women) and specific medical treatment. HCQ use was defined as use >6 months.

Medical records, including results of immunological tests, were assessed within the local hospitals. Anti-cardiolipin IgG and IgM antibodies were tested by the ELISA technique in two hospitals. LA was tested using dilute Russel Viper Venom test (HemosIL LAC Screen/LAC Confirm) in one hospital and a quantitative test based on aPTT and Russel Viper Venom time in the other [6]. Features not described in the journal or blood tests not found in the local hospital database were considered missing data.

Statistical methods
Categorical data were analysed by cross-tables and chi-square tests. Fischer’s exact test and chi-square test were used as post hoc tests where appropriate. Continuous variables were compared by one-way analysis of variance (ANOVA) with two-sample t-tests as post hoc tests, or Kruskal–Wallis test with Mann–Whitney post hoc tests, depending on the distribution of the data. A P < 0.05 was considered statistically significant. All reported P-values for differences between the three groups were Bonferroni corrected if not otherwise specified.

Results
Fig. 1 summarizes the inclusion of patients in the study. A total of 594 potential SLE patients in Oslo were identified: 581 from the hospital discharge database, 12 from the SLE cohort of 1995 and 1 from the connective tissue registry at Oslo University Hospital, Rikshospitalet. Nine patients were excluded, including one patient who did not respond and eight patients who had insufficient data for a definite diagnosis. Of the remaining 585 cases, 60 were considered to have SLE but failed to meet the classification criteria, and 200 did not have SLE. The number of excluded patients in the subgroups was 180/407 (44%) in the rheumatology group, 75/109 (69%) in the non-rheumatology group and 5/69 (7%) in the multidisciplinary group. The exclusion frequency was significantly lower in the rheumatology group compared with the non-rheumatology group (P < 0.001), with an odds ratio (OR) of 2.8 (95% CI 1.8, 4.3). The most frequent reason for excluding patients in the rheumatology group was patients considered to have SLE but with failure to meet the criteria (46/180), followed by primary SS (21/180), UCTD (17/180) and MCTD (6/180). In the non-rheumatology group, the most frequent causes of exclusion were discoid lupus without systemic disease (12/75), SLE with failure to meet the criteria (9/75) and given the wrong ICD-10 code number (8/75). In both groups the remaining patients excluded were spread among many other diagnoses and symptoms.

Thus 325 (56%) patients were included in the final analysis: 227 in the rheumatology group, 34 in the non-rheumatology group and 64 in the multidisciplinary group. Of the 34 patients in the non-rheumatology group, 21 had been treated and followed by nephrologists, 8 by specialists in infection medicine and 5 by haematologists. No other speciality was single-handedly taking care of the SLE patients, although some patients had their HCQ started by dermatologists. Neurologists prescribed the medication for epilepsy and occasionally for neuralgic pain, but never treated patients with anti-inflammatory medication without collaborating with the rheumatologists.
Baseline characteristics
The main basic characteristics for patients within the three groups are shown in Table 1. The median time from first SLE symptom to diagnosis, and from first symptom to development of kidney disease, was similar within the three groups. There were a total of 23 JSLE patients (under the age of 16 years when diagnosed) (data not shown).

Clinical and immunological manifestations in the three groups
Table 2 summarizes the distribution of ACR criteria in the three different groups. The non-rheumatology group and multidisciplinary group showed a similar distribution of ACR criteria, except for LA ($P = 0.03$), which was higher in the non-rheumatology group. There was a tendency to

![Flow diagram for inclusion of patients in the study.](image)

**Table 1** Basic characteristics of rheumatology, non-rheumatology and multidisciplinary groups

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Rheumatology (n = 227)</th>
<th>Non-rheumatology (n = 34)</th>
<th>Multidisciplinary (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female, n (%)</td>
<td>207 (81)</td>
<td>26 (76)</td>
<td>58 (91)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>205 (90)</td>
<td>30 (88)</td>
<td>53 (83)</td>
</tr>
<tr>
<td>Age at first symptom, median (range), years</td>
<td>31 (8–82)**</td>
<td>23 (11–68)</td>
<td>22 (6–69)</td>
</tr>
<tr>
<td>Age in 2007, mean (s.d.), years</td>
<td>48 (16)</td>
<td>45 (16)</td>
<td>44 (13)</td>
</tr>
<tr>
<td>Number of ACR criteria, median (Q1; Q3)</td>
<td>5 (4, 6)**</td>
<td>5 (4, 7)</td>
<td>6 (5, 7)</td>
</tr>
</tbody>
</table>

* $P < 0.05$ vs non-rheumatology group, Bonferroni adjusted. ** $P < 0.05$ vs multidisciplinary group, Bonferroni adjusted. Q1: first quartile; Q3: third quartile.
a higher proportion of discoid rash in the non-rheumatology group.

Kidney transplant was significantly more frequent in the non-rheumatology group compared with the multidisciplinary group (10 (29%) vs 5 (8%); \( P = 0.015 \)). LN patients in the non-rheumatology group and the multidisciplinary group had a similar frequency of reduced renal function (68 and 60%, respectively) and nephrotic proteinuria (67 and 62%, respectively), while patients in the rheumatology group had a significantly lower frequency of reduced renal function (22%) and nephrotic proteinuria (25%). The proportion of patients with APS was 12% in the rheumatology group, 22% in the non-rheumatology group and 22% in the multidisciplinary group (data not shown).

Missing data in the non-rheumatology group

In the non-rheumatology group, no test results for aPLs could be found in 11 (32%) of the SLE patients, which was significantly \( (P = 0.001) \) higher compared with 4% of patients in the rheumatology group and 6% of patients in the multidisciplinary group \( (P = 0.003) \). These differences were also found when only patients diagnosed after 1998 were studied. No test results could be found for LA in 9 (26%) of the SLE patients in the non-rheumatology group. In the non-rheumatology group, investigations for aPLs were not performed in 8/20 (30%) of the patients with LN, 3/9 (33%) of those with thrombocytopenia, 4/10 (40%) of those with neurological symptoms and 7/14 (50%) of those with hypertension; however, aPLs were tested in 11/13 (85%) of those with a thromboembolic event and 8/9 (89%) of those with kidney transplant (data not shown).

Medical treatment

Table 3 shows lower use of most drugs in the rheumatology group compared with the non-rheumatology and multidisciplinary groups, except for HCQ (81%). The treatment was similar among SLE patients in the non-rheumatology and multidisciplinary groups, except for HCQ, which was significantly more often used in the multidisciplinary group (78%) than in the non-rheumatology group (12%) \( (P < 0.001; \text{Table 3}) \). The proportion of patients who used HCQ at the time of investigation was 60% in the rheumatology group and 55% in the multidisciplinary group, whereas none in the non-rheumatology group used HCQ. The proportions of HCQ never-users in the rheumatology and multidisciplinary groups were significantly higher in patients diagnosed with SLE before 1999 (18%) compared with those diagnosed after 1999 (10%).

Characteristics of the patients treated with HCQ

Of all the 325 SLE patients, 78% had used HCQ at some time. Among the four patients treated with HCQ, in the non-rheumatology group two had discoid lupus and two had a kidney transplant. In the multidisciplinary group, HCQ was given to 36/45 (80%) patients who had LN, 21/25 (84%) patients who had nephrotic proteinuria, 21/26 (81%) patients with reduced renal function, 3/5 (60%) patients with a kidney transplant and 15/22 (68%) with aPLs. Among patients with LN, 66% were users of HCQ. When excluding the non-rheumatology group, the use of HCQ was 86% among LN patients (data not shown).

Among users of HCQ there was significantly less thrombosis compared with non-HCQ users \( (P = 0.032) \) with an OR of 0.54 (95% CI 0.31, 0.95) (data not shown).

Discussion

The main aim of this study was to investigate any possible differences in diagnostic and treatment procedures
between rheumatologists and internists. This study revealed that internists did not routinely test all SLE patients for aPL and seldom used HCQ. Infrequent use of HCQ by internists has been observed in the USA [1, 2], but different routines in testing of aPLs has not been shown in previous studies.

The strength of this study is the comprehensive identification of SLE patients within the region. Multiple sources have been used for identification of patients, and the records of all but one SLE patient have been reviewed. Due to the way the health system is organized in Norway, general practitioners refer even patients with mild symptoms of SLE for second-line service, thus missed cases are likely to be few. Possible lost cases for this cohort are most likely to be mild SLE patients, from the internist group and not seen since 1998. The main limitation of the study is the retrospective design, depending on the quality of medical records reviewed, and, as shown, a number of cases had to be excluded due to insufficient information regarding the individual ACR criteria for SLE.

A lack of data does not necessarily imply that such manifestations were absent. Additionally, tests not performed, missing data and events not definitely associated with SLE were unfortunately registered under the same category. The small number of patients within the non-rheumatology group limited generalization regarding this group.

The misdiagnosed patients had a wide variety of other diseases and symptoms. Conceivably, this is due to the clinical heterogeneity of SLE, and that several SLE manifestations are shared by many other syndromes. As shown, only 56% given an ICD-10 code of SLE met the ACR criteria, a finding that is supported by previous SLE shown, only 56% given an ICD-10 code of SLE met the manifestations are shared by many other syndromes. As

**TABLE 3** Medical treatment since diagnosis in the three groups: rheumatology, non-rheumatology and multidisciplinary

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Rheumatology (n = 227, n (%)</th>
<th>Non-rheumatology (n = 34, n (%))</th>
<th>Multidisciplinary (n = 64, n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>179 (81*)</td>
<td>32 (97)</td>
<td>60 (94)</td>
</tr>
<tr>
<td>HCQ</td>
<td>196 (88**)</td>
<td>4 (12*)</td>
<td>50 (78)</td>
</tr>
<tr>
<td>AZA</td>
<td>71 (32*)</td>
<td>15 (45)</td>
<td>39 (61)</td>
</tr>
<tr>
<td>MMF</td>
<td>3 (1**)</td>
<td>6 (18)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>High-dose CS</td>
<td>49 (23***)</td>
<td>25 (76)</td>
<td>50 (86)</td>
</tr>
<tr>
<td>CYC</td>
<td>16 (7***)</td>
<td>13 (39)</td>
<td>30 (48)</td>
</tr>
<tr>
<td>RTX</td>
<td>3 (1**)</td>
<td>4 (12)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*P < 0.05 vs multidisciplinary group, Bonferroni adjusted. **P < 0.05 vs non-rheumatology group, Bonferroni adjusted. High-dose CS ≥ 60 mg or ≥ 1 mg/kg; RTX: rituximab.

transplanted patients and patients with a positive test for LA in the non-rheumatology group. Potentially, the reason for not referring these SLE patients to a rheumatologist could be fewer musculoskeletal complaints. Similarly, rheumatologists did not regularly include nephrologists in the treatment of LN, which can only partly be explained by less serious LN.

It is conceivable that SLE patients with milder symptoms are more likely to see non-hospital-based physicians [11], and therefore patients in the rheumatology group may not be included in some studies. Should nephrologists describe the LN population, they would have lost 27 patients only followed by rheumatologists, losing valuable information of the total spectre of LN. If only SLE patients seen by rheumatologists had been included in this study, only 34 (10%) of the patients would have been excluded from the analysis. However, not including these 34 patients we would have lost 10 of 15 transplanted SLE patients. This study demonstrates that if selection bias according to the profession of the follow-up doctors occurs, even a small number of patients can cause a considerable impact on the final results.

The lack of testing for aPL in 11 (32%) of the non-rheumatology group patients was an unexpected observation. Furthermore, in the 11 patients not tested, a high frequency of features often associated with APS was observed (thrombocytopenia, neurological symptoms and hypertension). However, patients with a thrombotic event or kidney transplantation had been tested frequently. To explain the difference in aPL testing among rheumatologists and internists, written routines of the local hospitals were reviewed. In the Nephrology Department at Oslo University Hospital, Rikshospitalet, testing for LA is a part of the routine when planning for kidney transplantation. Furthermore, suspected APS was the only written indication for aPL testing in both local immunological departments. It is tentatively concluded that unless the patient has a thrombotic event or kidney transplantation, testing for aPLs is not the routine among internists. aPLs were implemented in the 1997 ACR criteria [4], and testing is now recommended by the European League Against Rheumatism (EULAR) and ACR in all SLE patients.
Interpretation of the data should be made with great caution, given the retrospective character of the study. Although it looks like non-rheumatologists do not follow EULAR recommendations, it is noteworthy that they had more patients with aPLs than rheumatologists did. As tests for aPLs were less frequently requested in the non-rheumatology group, even in patients diagnosed after 1998, the findings suggest that these recommendations have not yet reached non-rheumatologists to the same extent. The lack of recording aPLs may have important implications for management of the disease for a number of reasons. First, significantly elevated aPLs can be considered to be a risk factor for a number of ailments, including thrombosis and pregnancy loss [14], chronic renal insufficiency in LN [15], graft loss and transplantation outcome[16], renal artery stenosis and renal vein thrombosis. Consequently, recording aPLs may lead to administration of anti-coagulants such as aspirin. The recent recommendations from EULAR advocate the use of low-dose aspirin in case of elevated aPL, especially if there are other co-existing risk factors for thrombosis [17]. Interestingly, the use of anti-coagulant may even reduce the incidence of LN [18]. Secondly, data regarding aPLs may help to interpret a patient’s new symptoms [19], such as diagnosing renal manifestations due to small-vessel vaso-occlusive nephropathy in patients with aPL vs nephritis due to exacerbation of SLE in patients not possessing aPLs [20].

In the present study, it was found that SLE patients in the rheumatology group used far less immunosuppressive drug treatment than patients in the two other groups. This is consistent with the findings of less serious disease in this group. HCQ, however, was frequently used in both the milder and the more severe group, where rheumatologists had been involved with the treatment. Also, others have failed to find an association between the use of HCQ and disease severity [2]. In total, 88% of patients in the rheumatology group and 78% in the multidisciplinary group have used HCQ, which possibly indicates that all SLE patients are offered treatment with HCQ. This is in contrast to the infrequent use of HCO by patients in the non-rheumatology group, in which only 12% of patients had ever used HCQ. Moreover, patients with LN used less HCQ than patients without LN, a result that has also been found by others [21, 22]. Our study indicates that lower use of HCQ among patients with LN might not be due to the kidney affection, but due to non-rheumatologists’ infrequent use of HCQ in general. Lower use of HCQ treatment by non-rheumatology sub-specialities is supported by recent studies [1, 2, 23], but not to the same extent. More use of HCQ by rheumatologists in comparison with internists may have several possible explanations. The results may be confounded by indication, as HCQ traditionally has been used for mainly skin and joint manifestations [24], which are typically manifestations seen by rheumatologists. Additionally, higher HCQ use among rheumatologists may also be explained by the difference in tradition, as rheumatologists were introduced early to anti-malarial agents for the treatment of RA [25, 26]. On the other side, nephrologists may use less HCQ because of multi-pharmacy among transplanted patients, or concern of aggravation of side effects related to prolonged hypoalbuminaemia or reduced renal function. Finally, treatment with HCQ after kidney transplantation may be considered less important due to low rates of lupus flares in such patients. However, the use of HCQ was also infrequent in the pre-transplanted period (data not shown). The results show important differences among doctors in the use of HCQ in SLE, especially in the treatment of patients with LN. HCQ is often referred to as the cornerstone of lupus therapy [27], and is increasingly recommended in most patients with SLE, starting as soon as the diagnosis has been made [28]. There is strong evidence for HCQ in preventing lupus flares and increasing long-term survival [28]. Interestingly, the use of HCQ among rheumatologists was significantly higher among incident cases after 1999, indicating increased emphasis on HCQ as a basic therapy for SLE. In conclusion, the present study shows an urgent need for a closer cooperation among internists and rheumatologists. Important work has been done, including the recent development of recommendations and quality indicators for evaluation and monitoring of SLE patients by an expert panel of rheumatologists, other internists, dermatologists and a nephrologist [12, 29]. In Oslo, regular meetings between nephrologists and rheumatologists and publications of common practice in treating LN are one of the initiatives [30]. Review of the two local laboratory web sites has started, making the current EULAR recommendations for aCL and LA testing in SLE patients easily available for all specialties. Considering the significant disparities in the management and treatment of SLE between specialties observed in the present study, development of effective strategies to eliminate such disparities is clearly warranted.

**Rheumatology key messages**

- Non-rheumatologists infrequently use HCQ for SLE.
- Non-rheumatologists do not routinely test all SLE patients for aPLs.
- Only 56% given an ICD-10 code of SLE met the ACR criteria.

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