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REVIEW

Adherence to Oral and Topical Medications in Cutaneous Lupus Erythematosus is not Well Characterized

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ABSTRACT

Introduction: Treatment adherence plays a large role in chronic dermatologic diseases and may play an important role in the outcomes of patients with cutaneous lupus erythematosus (CLE). We sought to gauge what is currently known about adherence to topical and oral medications in patients with CLE.

Methods: A review of MEDLINE was performed using a combination of the phrases "adherence", "compliance", "lupus", and "cutaneous". Studies were hand searched and prospective and cross-sectional studies evaluating medication adherence in patients with CLE and systemic lupus erythematosus (SLE) were included.

Results: Only two articles explored adherence in patients with CLE, while 17 articles discussed treatment adherence in patients with SLE. Depression was consistently cited as detrimental to adherence. The impact that race, ethnicity, and education has on adherence is unclear. Three studies noted a clear connection between adherence and disease activity, while two others did not. Few studies investigated methods that have improved adherence to treatment which have showed promise.

Conclusion: Much of what we know about adherence to medication in patients with lupus is limited to SLE. Although cutaneous symptoms are among the most common manifestations of SLE, cutaneous disease is often managed at least in part with topical agents, and adherence to topical treatment was not assessed in any of the articles, though one study investigated sunscreen usage in patients with CLE. Understanding adherence in patients with CLE may help contribute to better CLE treatment outcomes.

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a chronic dermatologic disease that frequently requires long-term treatment and follow-up. Patients with CLE suffer from scarring, dyspigmentation, erythema, scaling, itching, burning, and pain which can have a profoundly detrimental impact on quality of life (QoL) [1]. Although there is no current Food and Drug Administration approved treatment for CLE, managing these patients is generally quite complex, consisting of lifestyle modifications [2] coupled with topical and/or oral medications [3]. Patient adherence in chronic diseases is a critical problem, as adherence to medication decreases through the long course of illness and may be adversely affected by the complexity of treatment [4–6]. Poor adherence may result in poor treatment outcomes [7–9].

We reviewed the literature to gauge what is currently known about adherence to treatment in patients with CLE. However, since approximately 85% of patients with systemic lupus erythematosus (SLE) will suffer from cutaneous manifestations of the disease at some point [10], and since American College of Rheumatology SLE criteria can be made on the basis of cutaneous disease alone [11], we also included studies involving patients with SLE. The purpose of this study is to determine what is known about adherence to treatment in patients with CLE and SLE (with cutaneous disease) and to identify gaps in the current knowledge of adherence in patients with CLE to guide future research endeavors to improve patient adherence.

METHODS

A search of MEDLINE was performed from date of inception to March 2015 using a combination of the search terms: “adherence”, “compliance”, “lupus”, and “cutaneous”. The results of these searches were filtered to include prospective and cross-sectional studies examining patient adherence to medications in both CLE and SLE. Duplicate articles and those not available in English were excluded. Studies on SLE that focused on the impact of the non-cutaneous aspects of SLE (e.g., kidney failure, antiphospholipid syndrome) on patient adherence, and those that also focused on adherence in other diseases in addition to CLE or SLE were excluded to maintain a focus on cutaneous disease. The studies were screened through titles, after which articles of interest were further examined through abstracts. If the study was found to be potentially eligible after examination of the abstract, a full-text review was carried out to assess for inclusion.

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

A total of 19 studies met the inclusion criteria (Table 1). Only one article [12] explored treatment adherence in patients with CLE, while another study examined adherence to sunscreen in patients with CLE [13]. The remaining 17 articles discussed treatment adherence in patients with SLE. Among these

Table 1 CLE and SLE articles that evaluated adherence

References	Demographic	Type of disease involvement	Medication	Method	Adherence rates	Factors associated with adherence	Outcomes
CLE articles							
Gutmark et al. [13]	Cross-sectional study of 100 patients with CLE	Not specified	No medication; adherence to sunscreen was asked	Self-report questionnaire	32% of patients used sunscreen daily, 40% did not use sunscreen	Poorer adherence: Lower income Better adherence: Being married Higher education level	N/A
Frances et al. [12]	Multicenter prospective study of 300 patients with CLE	160 patients with discoid lupus erythematosus 86 patients with subacute CLE 52 patients with lupus erythematosus tumidus 26 patients with chilblain lupus 16 patients with lupus panniculitis 39% of patients also met ACR criteria for SLE	Hydroxychloroquine	Blood levels, self-report	10% of patients were non-adherent (below 200 ng/mL of hydroxychloroquine)	Poorer adherence: Body mass index, weight	Patients with higher median blood concentrations were more likely to experience remission Complete remission less likely in males and those with discoid lupus erythematosus
SLE articles mentioning skin disease							
Oliveira-Santos et al. [14]	Cross-sectional study of 246 patients with SLE	Joint Mucocutaneous Serositis Neurologic Renal Hematological	Glucocorticoids, antimalarials, immunosuppressants	Interview self-report	31.7% reported 100% adherence	Poorer adherence: Mucocutaneous manifestations Poor family support Low education Better adherence: Hematological alterations	N/A

Table 1 continued

References	Demographic	Type of disease involvement	Medication	Method	Adherence rates	Factors associated with adherence	Outcomes
Costedoat-Chalumeau et al. [15]	Prospective study of 143 patients with SLE	On day 0: 10 had skin rash 10 had acute glomerulonephritis 9 had central nervous system involvement 1 has pleuritic 1 had pericarditis	Hydroxychloroquine Other drugs in which adherence was not measured: Azathioprine, cyclophosphamide, methotrexate	Blood levels	Hydroxychloroquine levels in patients without flares: 1,128 ± 507 ng/mL For	N/A	Lower blood hydroxychloroquine levels are predictive of SLE flares Higher hydroxychloroquine levels were associated with a decreased risk of having a flare
SLE articles not mentioning skin disease							
Gross et al. [28]	Cross-sectional study of 94 patients with SLE	Not specified	Not specified	Self-report questionnaire	68% of patients reported	Poorer adherence: Concerns about medications	
Abdul-Sattar et al. [30]	Prospective study of 80 patients with SLE in Egypt	15 patients with pleuritic or pericarditis 23 patients with renal disorders 29 patients with neurological disorder 14 patients with hematologic disorder	Prednisone, hydroxychloroquine, azathioprine, cyclophosphamide, mycophenolate mofetil	Self-report questionnaire	52.5% had adherence rate ≥80%	Poorer adherence: Rural residency, lower education level, low socioeconomic status, higher disease activity, higher depressive symptoms, shorter disease duration	Patients with higher disease activity had poorer adherence

Table 1 continued

References	Demographic	Type of disease involvement	Medication	Method	Adherence rates	Factors associated with adherence	Outcomes
Marengo et al. [27]	Multicenter prospective study of 110 patients with SLE, 78 agreed to have adherence electronically monitored	Not specified	Hydroxychloroquine, prednisone, methotrexate, mycophenolate mofetil, azathioprine	MEMS and self-report questionnaire	24% of patients had an adherence rate ≥80%	Poorer adherence: Polypharmacy, depression	No statistically significant connection between SLE disease activity and adherence
Ting et al. [16]	Prospective study of 70 patients with childhood-onset SLE	Not specified	Hydroxychloroquine	Pharmacy refill, self-report, and blood levels	Pharmacy refill: 32% had adherence rate ≥80% Blood levels: 25% had sufficiently high levels (900 ng/mL hydroxychloroquine) Self-report: 80% (±20%) adherence	None specified for adherence to medication	Cellular text messages did not improve outcomes
Bennett et al. [33]	Cross-sectional study of 190 patients with SLE	Not specified	Not specified	Online self-report survey	67% adherence (±12%)	Poorer adherence: Attachment anxiety and avoidance Better adherence: Strong working alliance	N/A
Duvdevany et al. [25]	Cross-sectional study of 100 patients with SLE	Not specified	Hydroxychloroquine, glucocorticoids	Self-report questionnaire	4.53 ± 1.17, where 5 is almost always and 1 is almost never	N/A	Adherence significantly predicted levels of functioning, not disease activity (when other variables were controlled for)

Table 1 continued

References	Demographic	Type of disease involvement	Medication	Method	Adherence rates	Factors associated with adherence	Outcomes
Daleboudt et al. [26]	Cross-sectional study of 106 patients with SLE	Not specified	Hydroxychloroquine, prednisone, azathioprine, other immunosuppressants	Self-report questionnaire	86.7% ± 18.0% reported adherence rate	Poorer adherence: Younger age Pacific Island ethnicity Poor cognitive functioning Concerns for side effects	No connection between adherence and outcomes
Chambers et al. [24]	Cross-sectional study of 220 patients with SLE, 31 were interviewed	Not specified	Hydroxychloroquine, prednisone, azathioprine, methotrexate, mycophenolate mofetil	Self-report questionnaire	9.7 median (8.8–10) adherence on a scale of 1–10, 10 meaning always taking medications	Poorer adherence: Fear of side effects	N/A
Julian et al. [23]	Prospective study of 982 patients with SLE in Brazil	Not specified	Not specified	Self-report questionnaire	45.4% of patients reported forgetting to take medications at least some of the time	Poorer adherence: Recent disease flare, higher disease activity, polypharmacy, shorter disease duration, poorer cognitive function, severity of depressive symptoms, income below poverty	Higher disease activity and more disease flares in patients who reported poorer adherence
Chambers et al. [31]	Cross-sectional study of 75 patients with SLE in Jamaica	Not specified	Prednisolone, deflazacort, azathioprine, hydroxychloroquine, chloroquine sulfate, mycophenolate mofetil, cyclophosphamide, methotrexate	Self-report interview	56% of patients reported taking their medications more than 85% of the time in the previous 6 months	Poorer adherence: Inability to afford medication, poor availability of medications, fear of side effects	N/A

Table 1 continued

References	Demographic	Type of disease involvement	Medication	Method	Adherence rates	Factors associated with adherence	Outcomes
Koneru et al. [22]	Cross-sectional study of 63 patients with SLE	Not specified	Prednisone, hydroxychloroquine, methotrexate, mycophenolate mofetil, azathioprine	Self-report questionnaire, pill counts, pharmacy refills, physician ratings	Pharmacy refill: 61% of prednisone patients ≥80% adherent 49% of hydroxychloroquine patients ≥80% adherent 57% of patients on other immunosuppressants ≥80% adherent	Poorer adherence: Non-white race (only for hydroxychloroquine), single marital status, not understanding physician instructions Better Adherence: Higher education level (only for prednisone adherence)	N/A
Nived et al. [21]	Cross-sectional study of 100 patients with SLE	Not specified	Glucocorticoids, hydroxychloroquine, cytostatic drugs, sunscreen	Self-report questionnaire	Glucocorticoids: 93% reported always taking their medicine Hydroxychloroquine: 88% of patients reported always taking their medicine Cytostatic drugs: 91% of patients reported always taking their medicine Sunscreen: 38% reported always using sunscreen	Better adherence: Higher education level	N/A

Table 1 continued

References	Demographic	Type of disease involvement	Medication	Method	Adherence rates	Factors associated with adherence	Outcomes
Koneru et al. [29]	Prospective study of 55 patients with SLE	Not specified	Hydroxychloroquine and prednisone	Self-report questionnaire, pill counts, pharmacy refills, physician ratings	Pharmacy refill: 36% of patients on prednisone had <80% adherence 51% of hydroxychloroquine patients were non-adherent	Not Specified	N/A
Costedoat-Chalumeau et al. [17]	Prospective study of 203 patients with SLE	33% of patients had antiphospholipid syndrome	Hydroxychloroquine	Blood levels and self-report interviews	7% of patients reported not taking their medication in interviews	Poorer adherence: Concerns for potential side effects	Non-adherence was a risk factor for SLE flares 50% of non-adherent patients had disease flares compared to 15% of the rest of patients
Mosley-Williams et al. [20]	Cross-sectional study comparing adherence rates between 68 African Americans and 54 white patients	Not specified	Steroids, hydroxychloroquine, cyclophosphamide	Self-report interview	30.8% of African Americans and 23.4% of white patients reported never failing to take their medications. 9.2% of African Americans and 10.6% of white patients reported failing to take their medication "all of the time"	Poorer adherence: Depression (higher association with adherence in African Americans) Better adherence: In white patients: belief in the medication and trust in the physician	N/A

CLE cutaneous lupus erythematosus, SLE systemic lupus erythematosus, *MEMS* Medication Event Monitoring Systems, *ACR* American College of Rheumatology

studies, only two specifically mentioned skin manifestations [14, 15].

Measuring Adherence in Lupus Erythematosus

A large contributor toward the wide range of adherence rates observed in these studies (Table 1) was likely due to the different methods used to assess adherence (Table 2). The different methods can be characterized as either subjective (e.g., self-report) or objective (e.g., drug blood assays, electronic monitoring). Measuring hydroxychloroquine blood concentration is an objective method that has been employed by several studies used to determine adherence levels in SLE and CLE patients [12, 16, 17]. Objective assessments of adherence are preferred, since patients often overestimate their own adherence [18]. However, Ting et al. [16] used several methods to assess adherence, and noted that self-reported adherence correlated with adherence based on hydroxychloroquine blood concentration and adherence assessed through pharmacy refill data.

One challenge that is encountered when assessing adherence through blood assays is

Table 2 Advantages and disadvantages of the methods used to determine adherence in SLE and CLE

Methods of measuring adherence in CLE and SLE					
	MEMS	**Hydroxychloroquine blood assays**	**Pharmacy refill information**	**Pill counting**	**Self-report**
Pros	Can be used on topical and oral medications	Accurate in recognizing non-adherent patients [17]	Inexpensive	Inexpensive	Inexpensive
	Provides exact date and time medication was opened [27]				
Cons	Expensive [29]	Not readily available [29]	Time consuming [29]	Cumbersome [29]	Subjective
	Patients may not use medication even if they open the bottle which can overestimate adherence [27]	Occasional missed doses may not be noticed because of long half-life			Doctors and patients overestimate adherence levels [29]
		Cannot be used for topical medications	Cannot be used for topical medications	Cannot be used for topical medications	
Useful applications	Research	Research or clinical practice	Research	Research	Survey studies or clinical practice

CLE cutaneous lupus erythematosus, *SLE* systemic lupus erythematosus, *MEMS* Medication Event Monitoring Systems

that adherence tends to increase closer to when the patient's appointment is, the so-called "white coat compliance" [17, 19]. However, hydroxychloroquine has an exceptionally long 40 day half-life and small inter-day variation in blood levels, which allows physicians to assess long-term adherence to the medication with reasonable accuracy [12, 17]. Furthermore, unscheduled blood-level measurements have been also used to circumvent the issue of white coat compliance [17]. Unfortunately, few drugs have such a long half-life that would enable practitioners to know with confidence if their patients are truly adhering to the medication, making this not applicable for other systemic medications used to treat CLE or cutaneous disease in SLE.

Additional methods of measuring medication adherence in SLE included physician and patient questionnaires or ratings, pill counting, Medication Event Monitoring Systems (MEMS), and using pharmacy refill information [14, 20–28]. The use of MEMS is an objective method of assessing patient adherence to medications in SLE, which uses microchips to determine when patients have opened and closed their medication bottles [22, 27]. MEMS can be used for topical medications as well as oral medications, which allows for its utilization in topical treatments for SLE and CLE, which cannot be done in methods such as blood assays or pharmacy refill information [6].

Pill counting involves patients bringing in their medication to their appointments and subsequently having their remaining pills counted to determine their level of adherence. Acquiring pharmacy refill data can show the level of patient adherence by seeing if patients are refilling their medications in a timely manner. One study utilized multiple methods including blood assays of hydroxychloroquine, questionnaires, and pharmacy refill information to better assess adherence in adolescent patients with SLE [16]. Pharmacy refill information has also been used as the criterion standard to base the accuracy of other methods of measuring adherence, such as patient and physician questionnaires, and pill counts [29]. Of these methods, pill counting was the least effective in determining adherence [29]. Using pharmacy refill information to determine adherence to topical medications would also prove challenging, because patients may use varying amounts of medication depending on the extent of cutaneous disease they have. While there are numerous ways of assessing adherence, MEMS appear to be the most ideal for clinical trials, whereas pharmacy refill information strikes a good balance between cost, practicality, and objectivity, making it a good choice for more mainstream use.

Factors Contributing to Non-Adherence

Many factors have been postulated to have an impact on treatment adherence in patients with SLE and CLE (Table 1). The impact that race/ethnicity has on medication adherence in SLE is controversial. Two studies noted no statistically significant difference in adherence to medication between white patients and ethnic minorities suffering from SLE. One study in Brazil [14] noted that white race was a factor that improved adherence, while others found that non-white race was a risk factor for lower adherence to hydroxychloroquine [14, 20, 22, 27]. While race and ethnicity have not been definitively shown to impact adherence to medication in SLE, socioeconomic factors can contribute [30]. Affordability of medication can also play a large role in adherence [31].

Different factors may play a role in adherence to medication between white and black patients. There was a substantial disparity

in income between the groups, and the differences between the groups' reasons for poor adherence to medication were eliminated after controlling for income level [20]. Education level was another factor that may have an effect on medication adherence in patients with SLE, with lower levels of education thought to result in poorer adherence to medication [14, 22–24, 30]. However, lower education levels were associated with worse adherence to medication in only two of five studies [14, 22]. In a study of CLE patients, Gutmark et al. [13] noted that adherence to sunscreen was better in patients that had a higher educational level, and lower in patients with lower income. Conversely, another study noted that higher education levels and those with lower income levels were associated with lower levels of adherence, although the population in this study were all of low socioeconomic status [28]. Depression is a consistent factor that negatively impacts adherence to medication in SLE [20, 23, 25, 27, 30]. SLE is thought to directly cause depression either by its direct impact on the brain and/or due to the chronic inflammatory process [32]. Furthermore, depression, as well as other neuropsychiatric manifestations of SLE, can cause cognitive impairment which can lead to patients forgetting to take their medications [23, 26]. Many other reasons contribute to poor adherence to medication in patients with SLE (Table 1).

Adherence, Disease Activity, and Outcomes

Poor adherence to medication can result in poor outcomes in patients with SLE, as it is associated with increased disease activity as well as increased risk of disease flares [15, 17, 23, 30]. Patients with SLE who struggled with adhering to their medications had a decreased level of functioning [23]. Presumably, poor adherence to treatment leads to increased disease activity which can profoundly decrease functioning. Increased disease activity was not only a result of poor adherence, but also a risk factor to it [17, 23]. Higher blood levels of hydroxychloroquine led to higher levels of remission in patients with CLE, implying that increased adherence in these patients was associated with better outcomes [12].

While there is likely a clear association between adherence and outcomes, a couple of studies did not find this connection. Marengo et al. [27] noted that while their patients improved after 2 years of adherence monitoring, there was no statistically significant association between adherence and SLE disease activity. Daleboudt et al. [26] found no connection between disease severity and self-reported adherence rates.

Methods used to Improve Adherence

Several studies examined ways of improving adherence in patients with SLE. One barrier to treatment adherence in patients with SLE, and adherence to sunscreen in patients with CLE is forgetfulness [13, 23]. One study attempted to overcome this using cellular text messaging to remind patients with childhood-onset SLE to take their medications; however, there was no improvement in adherence to treatment noted among the adolescents studied [16]. Hydroxychloroquine blood levels were utilized to identify patients who were non-adherent to hydroxychloroquine and found that confronting these patients with their non-adherence and counseling them regarding the characteristics of hydroxychloroquine treatment led to a significant increase in most of these patients' hydroxychloroquine blood

concentration [17]. The physician–patient relationship plays a crucial role in patient adherence to medication in SLE [33]. A strong working alliance, which sets treatment goals and tasks that are agreed upon between the provider and the patient, was correlated with increased adherence to medication in SLE [33]. Patient adherence to medication is a pervasive problem that continues to be tackled and overcome in patients with SLE.

DISCUSSION

Poor adherence is a huge problem in dermatology, and it is an especially difficult in chronic diseases [19]. Such diseases in dermatology such as acne and psoriasis have been extensively studied with regard to treatment adherence [34–36]. Despite its chronicity and impact on QoL, CLE has not been studied to nearly the same extent.

Accurately assessing medication adherence in patients with CLE and SLE is of great importance because doing so can distinguish patients who are non-responsive from those who poorly adhere to treatment [12]. This can prevent poorly adherent patients from being placed on more toxic medications [12]. Among the methods used in monitoring adherence to treatment in SLE and CLE, measuring hydroxychloroquine concentrations in the blood and utilizing MEMS stand out as potential methods of gauging treatment adherence; however, its use is mainly limited to clinical studies [29]. MEMS also allows for determining the time and date the medication was used, which is a feature that none of the other methods used can offer, and it allows for deeper insight into the specific adherence patterns that patients exhibit [29].

The long half-life of hydroxychloroquine makes blood levels a useful tool for assessing adherence [15]. Patients tend to take their medications more consistently around the time of office visits [19], limiting the value of blood levels for drugs with short half-lives. Several means of improving adherence to treatment in SLE were also investigated. The doctor–patient relationship can be used to improve adherence by engaging patients with adherence problems in a non-threatening way and discussing treatment characteristics. Creating a strong working alliance between patients and providers is another way the doctor–patient relationship can improve adherence to medication [33]. Text message reminders did not boost adherence to treatment [16]. Additional studies investigating how adherence to treatment can be further improved are warranted.

The majority of what is currently known about adherence to treatment in CLE is based on studies done on patients with SLE [37]. While there is significant overlap between SLE and CLE, only two SLE studies mentioned cutaneous manifestations. Of the two studies, Oliveira-Santos et al. [14] noted that the presence of mucocutaneous manifestations of SLE was associated with decreased rates of adherence. The other study conducted by Costedoat-Chalumeau et al. [15] in 2006 noted that rashes were one of the findings associated with disease flares in patients with poor adherence to hydroxychloroquine. The rest of studies failed to mention what portion of SLE patients in their study were suffering from cutaneous disease, which leads to further difficulty in utilizing the results of these studies to further our knowledge of adherence in CLE patients, and in those with SLE suffering from cutaneous disease. While this could be viewed as a limitation of our study, it also demonstrates the current need for studies examining the impact of cutaneous disease on adherence in patients with SLE. However, it is

likely that many (if not all) of these studies were comprised of patients with cutaneous disease, since the majority of patients with SLE will suffer from some sort of cutaneous manifestation of their disease at some point [10].

The study conducted by Frances et al. [12] was one of the two studies we found that investigated adherence to treatment in patients specifically with CLE. This study only examined adherence to hydroxychloroquine which is a medication that is taken orally. The other study [13] investigated adherence to sunscreen. However, no studies mentioned adherence to topical medications in treating CLE or cutaneous disease in patients diagnosed with SLE. While systemic therapy is essential in controlling more severe disease, topical and localized treatments are often used in the treatment of CLE and cutaneous manifestations of SLE [3]. This lack of knowledge is especially disconcerting because adherence to topical medications is lower than that of systemic medications [38, 39].

CONCLUSION

Much of what we know about adherence to medication in patients with lupus is limited to SLE. Although cutaneous symptoms are among the most common manifestation of SLE, cutaneous disease is often managed at least in part with topical agents, and adherence to topical treatment was not assessed in any of the articles, though one study investigated sunscreen usage in patients with CLE. Understanding adherence in patients with CLE may help contribute to better CLE treatment outcomes. Further studies are required to expand our knowledge of adherence to both topical and systemic medications in patients with CLE and cutaneous manifestations of SLE.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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