Medication adherence in systemic lupus erythematosus during Brazilian COVID-19 pandemic

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Abstract

Background: Patients with chronic diseases are potential candidates for inadequate follow-up of drug therapy, tending to incur damage to the intended results. This deserves greater attention in the pandemic period, as they are in the considered risk group.

Methods: We aim to assess Treatment Adherence Measure and analyze associations with characteristics related to the patient, treatment, disease, health professionals and service, and sociodemographic issues in patients with Systemic Lupus Erythematosus (SLE). W conducted a cross-sectional study with a sample of 116 participants, whose data were collected through individual interviews and review of medical records, during the first months of the COVID-19 pandemic in Brazil. Adherence was measured using the Treatment Adherence Measure, and associations were evidenced through described and inferential statistics.

Results: The percentage of adherent patients was 55.2%. An association was found between MTA (Medication Treatment Adherence) and physical exercise practice ($p = 0.032$), and difficulties with treatment ($p = 0.002$). Conclusion: Participants who did not practice physical exercise were 3.71 times more likely to not adhere to the treatment. Individuals who identified difficulties in the treatment were 3.43 times more likely to not adhere to the treatment; we believe that the pandemic may have influenced this result. More targeted studies are needed to measure the impact on MTA in these patients.

Introduction

World Health Organization (WHO) considers that non-medication therapy represents a global public health problem, generating a great impact on society. During the treatment of chronic diseases in developed countries, long-term therapy is estimated at approximately 50%. It is assumed that adherence rate is even lower in developing countries, mainly due to the socioeconomic context, which can difficult access to education and health services.[1] Non-medication adherence could contribute to increase the number of hospitalizations, loss of autonomy, mobility, and, consequently, quality of life. In this context, increases in either morbidity or mortality rates are possible consequences.[2]

Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease that can compromise different organs and multiple systems.[3] The clinical presentation of SLE can range from mild disease without impaired vital organs to severe cases.[4] Drug treatment is organ-specific and includes corticosteroid therapy and combination of different immunosuppressive and immunomodulatory drugs, especially in the most severe cases.[5] In addition, patients with SLE often have many comorbidities such as osteoporosis, diabetes, obesity, in addition to increase cardiovascular risk, requiring even more medications,

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worsening the polymedication treatment scenario.[5] SLE has an estimated cost of US\$ 3735–US\$ 14,410 per patient per year with direct costs related to outpatient and hospital therapies.[6] These costs are not calculated regarding a non-adherence context.

World Health Organization conceptualizes adherence as the degree to which the individual's behavior, represented by medication intake, diet follow-up, and adoption of lifestyle changes, agrees with the recommendations made by the health professional.[1] Adherence is considered a multidimensional phenomenon that culminates as a product of the interaction of five main groups, and the factors related to the patient are only one determinant. The dimensions proposed are the following factors: 1—socioeconomic, 2—related to the patient himself, 3—to the disease, 4—to treatment, and 5—to the system and health team.[1]

Studies of drug therapy adherence in patients with rheumatic diseases are scarce in developing countries, including Brazil, for SLE patients.[7] The majority are in developed countries, which present different realities from Brazil that has a large socioeconomic imbalance with a huge disparity between "extreme poverty" and "extreme wealth" with poor access, for many patients, to health services.[8] In addition, there are no studies published on SLE adherence in a COVID-19 pandemic context, especially in populations with low level of socioeconomic development.

Thus, verify the Medication Treatment Adherence (MTA) in SLE and its associated factors, during COVID-19 pandemic, can contribute to the development of intervention strategies in this new world scenario, helping to improve the quality of life and long-term prognosis of these patients. For this purpose, we carried out a study during the first 6 months of the COVID-19 pandemic in a region of low human index development of Brazil.

Materials and methods

Study design and population

We performed a cross-sectional study with SLE patients who fulfilled the classification criteria for SLE made by the American College of Rheumatology (ACR)[9] and were undergoing drug treatment for SLE. A convenience sample of consecutive adult patients with SLE was recruited over 24 weeks when patients attended their outpatient. The participants' physicians were only involved in the recruitment process and the interview was done before the beginning of consultation by a health professional non-integrant of the medical team. One hundred and 16 patients with SLE, aged between 18 and 65 years old, were selected from the Lupus Outpatient Clinic at the Professor Alberto Antunes University Hospital (HUPAA), Federal University of Alagoas (UFAL), Brazil. This SLE outpatient clinic is a reference unit for lupus care in the state of Alagoas, northeast of Brazil. All patients were treated by rheumatologists and the data was collected during COVID-19 pandemic period, from March to August of 2020.

Ethical aspects and procedures

This study was approved by local Ethics Committee for Research of the Federal University of Alagoas (No. 3.606.129; CAAE: 18118619.5.0000.5013) and complied with the Helsinki Declaration. Written informed consent was obtained from each participant.

Data collection

Data were obtained through direct interview of the patients and completed with review of patient charts. The aims of the interview were to measure therapeutic adhesion and its associated factors.

We used a structured, coded questionnaire, and a sheet for collecting data from the patient chart. We focused on information pertaining to clinical manifestations, aspects of the disease, and medicines prescribed in the last consultation. This questionnaire was developed according to the medical literature about treatment adherence in chronic diseases.

It was used a questionnaire to verify therapeutic adherence: the Measurement of Adherence to Treatment (MAT).[10] This instrument consists of seven items that assess the individual's behavior in relation to the daily use of prescribed medications for chronic diseases. The responses to the items are obtained from a six-point Likert scale, where "1" corresponds to "Always" and "6" to "Never." The mean value of the seven items is obtained. If the value obtained is between five and six, it is classified as compliant and below five classified as non-adherent.

In order to identify factors associated with adherence, a questionnaire was elaborated considering the five dimensions proposed by WHO that included: characteristics of the treatment and disease; factors related to social and economic issues; aspects to health professionals and services and those related to the patients. Furthermore, it was also evaluated the association between medication adherence and activity of SLE disease, organ damage due to SLE, and quality of life scores.

It was used the Brazilian Economic Classification Criteria of the ABEP (Brazilian Association of Research Companies) for the economic classification.[11] The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), in its 2K version, was used to assess disease activity.[12] The Systemic Lupus International Collaborating Clinics/American College of Rheumatology—Damage Index (SLICC-ACR) was performed to verify organ damage.[13] The 12-item Short Form Survey (SF-12) was used to assess different dimensions of life quality, considering the

Table 1. Sociodemographic and lifestyle habits characterization.

	General, N=116	Adherent, n= 64	Non-adherent, n= 52	p-value
Sociodemographic characteristics				
Age, years (Mean/SD.)	36.5 (11.3)	34.2 (11.6)	39.4 (10.3)	0.007[a]
Female[A](%)	111 (95.7)	60 (93.8)	51 (55.8)	0.254
Non-Caucasian ethnicity (%)	96 (82.8)	52 (81.2)	44 (84.6)	0.633
Schooling >10 years old (%)	80 (69.0)	45 (70.3)	35 (67.3)	0.728
Economic status (%)				
Poverty	54 (46.5)	25 (39.1)	29 (55.8)	0.073
Married (%)	66 (56.9)	36 (56.3)	30 (57.7)	0.876
Living arrangement (%)				
Accompanied (a)	111 (95.7)	62 (96.9)	49 (94.2)	0.486
Residency (%)				
Inlandy city	65 (56.0)	37 (57.8)	28 (53.8)	0.669
Income (%)				
Yes	76 (65.5)	44 (68.8)	32 (61.5)	0.416
Unemployed (%)	97 (83.6)	52 (81.2)	45 (86.5)	0.444
Internet access (%)	105 (90.5)	61 (95.3)	44 (84.6)	0.051
Life habits				
Smoking (%)	3 (2.6)	1 (1.6)	2 (3.8)	0.441
Alcohol consumption (%)	12 (10.3)	5 (7.8)	7 (13.5)	0.320
Exercise practice[B] (%)	22 (19.0)	18 (28.1)	4 (7.7)	0.005**

[a]*Mann–Whitney Test* ** chi-square test.
[b]**OR=** 3.4 (0.368–31.395)[B] **OR=**4.696 (1.477–14.925).

individual's perception in the last 4 weeks: Limitations in physical activities because of health problems; limitation in social activities because of physical problems; limitations in usual role activities because of physical health problems; bodily Pain; general mental health; vitality; limitations in usual role activities because of emotional problems; general health perceptions organized into physical component and mental component.[14]

Statistical analysis

The statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS)—version 22.0. Quantitative data were statistically described in terms of mean and standard deviation (SD) or median (range) while qualitative results were presented as number and percentage. The Shapiro–Wilk Test was used to determine the normality of the distribution of numeric variables. Student's test was performed to compare quantitative variables with normal distribution between groups, and for quantitative variables with non-normal distribution, the non-parametric Mann–Whitney test was used. Pearson's chi-square test (χ^2) was used to compare groups (adherent and non-adherent) involving qualitative categorical variables. Binary Logistic Regression was performed to determine predictive factors associated with non-adherence of medication in SLE. A two-tailed probability value (p-value) less than 0.05 was considered statistically significant.

Results

A total of 116 patients were included. The sociodemographic, life habits, and patient's clinical characteristics are shown in Table 1 and Table 2. We did not find significant association between sociodemographic and clinical characteristics with therapeutic adherence.

Table 1 shows a lower mean age was observed in adherent patients. A higher frequency of individuals who practiced exercises among adherents was also observed.

The groups were similar from a clinical perspective. Table 2 shows the clinical characterization.

We also assess prior knowledge of SLE as well as its information sources such as healthcare professionals, social media, and chat apps. No significant association was found between these variables and MTA (Supplementary Table I). Regarding the care regimen, only the variable perception of treatment difficulties was associated with MTA (Supplementary Table II). Regarding the therapeutic regimen and access to drug therapy, no association with MTA was found (Supplementary Table III). The adverse event that showed an association with adherence was headache (Supplementary Table IV). With regard to access to services and health professionals, the variable means of access was associated (Supplementary Table V).

There was influence from both intentional and unintentional items. Non-adherent scans had a mean lower than five in all items; on the other hand, the adherents presented an average lower than five only in item two of the MAT. It is questionable

Table 2. Clinical characteristics.

Characterization	General, N=116	Adherent, n=64	Non-adherent, n=52	p-value
Disease duration (%)				
≤10 years	103 (88.8)	59 (92.2)	44 (84.6)	0.199
Pregnancy (%)	9 (8.1)	6 (10)	3 (5.9)	0.443
Comorbidities presence (%)	62 (53.4)	34 (53.1)	28 (53.8)	0.938
Previous hospitalization (%)	80 (69.0)	48 (75.0)	32 (61.5)	0.119
SLEDAI≥ 4 (%)	80 (69.0)	44 (68.8)	36 (69.2)	0.956
SLICC≥ 1 (%)	56 (48.3)	29 (45.3)	27 (51.9)	0.479
SF-12 (Mean/SD.				
Mental component [a]	35.5 (9.5)	34.7 (9.8)	36.6 (9.0)	0.183
Physical component[b]	38.3 (10.7)	37.4 (11.0)	39.4 (10.3)	0.328

[a]The *Mann–Whitney*.
[b]*Student's t test*.

Table 3. MAT scale domain values in adherent and non-adherent groups.

MAT items	Adherent, n= 64 Mean (SD)	Non-adherent, n= 52 Mean (SD)	IC 95%	p-value
1- Have you ever forgotten to take your meds?	5.03 (0.85)	3.78 (1.14)	0.87–1.61	<0.01
2- Have you ever been careless about taking your meds?	4.45 (1.08)	3.38 (1.20)	0.64–1.49	<0.01
3- Have you ever stopped taking your meds because you felt better?	5.75 (0.64)	4.75 (1.06)	0.66–1.33	<0.01
4- Have you ever stopped taking your medications on your own initiative after feeling worse?	5.81 (0.46)	4.48 (1.21)	0.97–1.68	<0.01
5- Have you ever taken one or more tablets on your own initiative after feeling worse?	5.84 (0.51)	4.88 (1.06)	0.63–1.27	<0.01
6- Have you ever stopped treatment for letting your meds run out?	5.04 (0.95)	4.38 (1.10)	0.27–1.04	<0.01
7- Have you ever stopped taking your medications for any reason other than the doctor's advice?	5.42 (0.70)	4.53 (0.87)	0.58–1.18	<0.01

Table 4. Predictive factors associated with non-adherence of SLE medication.

Dependent measures	B	S.E.	Sig	OR	95% C.I. Inferior	95% C.I. Superior
Age	−0.030	0.020	0.132	0.971	0.934	1.009
Practice of physical exercise	1.312	0.610	0.032	3.713	1.122	12.281
Difficulties in treatment	1.233	0.406	0.002	3.432	1.549	7.605
Headache	0.603	0.431	0.162	1.828	0.785	4.255
Means of access to the health service	−0.833	0.582	0.152	0.435	0.139	1.360

if unintentional factors would be as relevant as it was in this research if there was no pandemic in course (Table 3).

A binary logistic regression was performed to verify whether age, claim to have difficulty in continuing treatment, practicing physical exercise regularly, reporting headache, and reporting having difficulties in accessing the service where it is treated are predictors of non-medication treatment in SLE. The model containing the above variables was significant (X^2 (1)= 22.46; $p < 0.001$; R^2 Negelkerke = 0.26). Reporting difficulty in continuing treatment (OR= 3.43; CI 95% 1.55–7.60) and not performing regular physical exercise (OR = 3.71; CI 95% = 1.12–12.28) were significant predictors of non-adherence to medication treatment in SLE (Table 4).

Discussion

In response to the COVID-19 pandemic, countries have sought to control SARS-CoV-2 transmission by restricting population movement.[15] Social-distancing, case isolation, and shielding have been widely used to limit community-level transmission of SARS-CoV-2 and protect vulnerable group.[15] Early in the epidemic, an alert was indicated for patients with chronic diseases that could be at increased risk for severe illness. Health services adopted protocols to minimize risk of contamination, especially of these groups; however, the population remained afraid to seek care due to the pandemic.

We evaluate SLE medication adherence during COVID-19 pandemic and its association with five dimensions proposed by WHO for adherence in chronic diseases (aspects related to the patient, the disease, economic and social aspects, health professionals and services, and the characteristics of the proposed treatment).[1] In developed countries, WHO estimated that adherence among patients suffering chronic diseases averages 50%.[1] Our research was carried out in a poor region of Brazil, in a tertiary care hospital during a pandemic period. Poor adherence in developing countries is assumed to be even higher given the paucity of health resources and inequities in access to health care. In despite of this context, the percentual of adherents in our study was 55.2% that was equivalent than that expected for chronic diseases treatment adherence even in developed countries.[1] This observed adherence rate is comparable to those reported in other international studies of SLE before COVID-19 pandemic, as described in a recent systematic review from Mehat et al.[16] who found adherence rates between 49.8 and 86.7%. There are only few previous studies in Brazil reporting rates of adhesion in SLE medication treatment. Their rates of adhesion varied from 31.7 to 45.9%.[7,17] Considering the potential severity of SLE and the data from studies performed in developed countries, although the adhesion that we found is compatible with studies performed before the pandemic period, this adhesion rate is far from the ideal, once almost half of patients were non-adherents.

We used MAT questionnaire to measure adhesion. It corresponds to a scale composed by two behavioral categories of non-adhesion (intentional and non-intentional), and involves the most significant aspects of other scales. Intentional non-adherence refers to that associated with the patient's motivation, while non-intentional is driven by the lack of capacity or resources to take medications. The underlying reasons for intentional and unintentional non-adherence are not entirely independent and some types of unintentional non-adherence, for example, forgetfulness, are logically more likely when motivation for medication is low.[18,19] We found low rate of both adherence categories.

Regarding the association of non-adherence with factors contained in the five dimensions of WHO, we demonstrated

association only with physical exercises and self-perception of difficult to treat SLE.

Many studies have found association between adherence and depressive and anxiety disorders.[20,21,22,23,24] In the study proposed by Heiman,[24] depression was strongly correlated with poor medication adherence. That work suggested that screening for depression should be considered in all patients with SLE, particularly in those patients who do not adhere to treatment. A study carried out in 2019 that aimed to analyze the relationship between physical activity, depression, and adherence to antiretroviral therapy among people with HIV infection, a significant relationship was found between physical activity and adherence to antiretroviral drugs, highlighting the importance of physical activity in disease management.[25] Our study was not addressed to analyze the impact of psychiatric diseases or self-esteem in adherence, but these disorders can have their impact attenuated by physical activity.[26,27,28] Whereas physical activity is designed to promote pleasurable and beneficial experiences, it can be considered an important element of a behavioral activation. So, physical activity could have a direct influence both on how the person with SLE can face their routine, as well as on their level of independence and sense of well-being.[29] Non-adherence to treatment can be intentional, that is, the patient himself decides not to follow what was prescribed/advised or unintentional, in which, despite the patient's desire to follow what was recommended, he has limitations for doing so. This hypothesis could justify the data of our study in which patients who did not practice physical exercise were 3.71 times more likely not to adhere to drug treatment.

Our questionnaire included a subjective question that aims to have a high sensitivity to identify any reason that the patient considers relevant and that could interfere in his medication treatment and that was not contemplated in other questions made. This outcome was associated with probability of non-adhesion in 3.43 times. Despite the lack of specificity, once many other questions were made to investigate the main WHO domains, the COVID-19 pandemic may have influenced this result. It is reasonable to think that COVID-19 pandemic is associated mainly with non-intentional factors, interfering especially in the access of tertiary healthcare units, which, in Brazil, are the main responsible for medications distributions and consultations for SLE patients. Furthermore, during the period of this study, hydroxychloroquine was recommended to treat COVID-19 in Brazil, causing its scarcity for SLE sometimes, which could also have contributed for the non-intentional non-adherence. During the first 6 months of pandemic in Brazil, there was no widely infrastructure for medical teleconsultations, so human mobility restriction probably interfered in the treatment adherence. Moreover, in despite of safety patient protocols adopted, the fear of getting infected with SARS-COV-2 in the health units also could have contributed with intentional non-adherence,

once that the individuals were not having medical appointments regularly, and getting their medication. So, probably COVID-19 pandemic interferes in both non-intentional and intentional factors.

It was not evaluated the incidence of COVID-19 and its complications in the patients studied or in their families, becoming difficult to conclude if patients who eventually became infected had even worse adherence. We did not analyze the adherence of each medication singly and we do not have adherence data from previous studies designed with the same population, impairing to affirm the true impact of hydroxychloroquine prescription for COVID-19 in the adherence. We also did not perform a specific questionnaire to evaluate physical activity, but in the context of strong association with this outcome and rational hypothesis to explain the find, we suggest a specific research to better understand the impact of physical activity in SLE adherence.

The interview was to be done before the beginning of consultation by a health professional non-integrant of the assistance medical team minimizing information bias. However, indirect methods to measure adhesion, according to some authors, may incur an overestimation of the adhesion levels, because there is dependence on the patient's report, which can hide how the treatment was performed.[30]

Finally, considering a new world scenario in which COVID-19 can become an endemic disease in the next years, and the many ways in which it can interfere on health care in individuals with SLE, we need more studies driven to measure the impact on therapeutic adhesion in these patients. From new evidences, maybe WHO would need to consider the impact of pandemic as a single factor on therapeutic adhesion in SLE.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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