COVER PAGE

Official Title: Relevance of Monitoring Blood and Salivary Levels of Drugs Used in Rheumatic Autoimmune Diseases

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HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP FREE AND INFORMED CONSENT TERM

IDENTIFICATION DATA OF THE RESEARCH SUBJECT OR LEGAL GUARDIAN

1. NAME:.....

ID No:..... SEX: M ☐ F ☐

DATE OF BIRTH: ...../...../.....

Address:..... Nº: ..... Fit:.....

Neighborhood:..... City:.....

Zip code:.....PHONE:DDD (.....) .....

2. LEGAL GUARDIAN.....

NATURE (degree of kinship, tutor, healer, etc.):.....

ID No: ..... SEX: M ☐ F ☐

DATE OF BIRTH: ...../...../.....

Address:..... Nº: ..... Fit:.....

Neighborhood:..... City:.....

Zip code:..... PHONE: DDD (.....) .....

RESEARCH DATA

1. TITLE OF THE RESEARCH PROTOCOL:

THEMATIC PROJECT: EVALUATION OF THE RELEVANCE OF BLOOD LEVELS OF DRUGS USED IN RHEUMATIC AUTOIMMUNE DISEASES IN THE MONITORING OF THE SAFETY/EFFICACY OF THERAPY, DISEASE ACTIVITY AND ADHERENCE TO THERAPY.

SUBPROJECT: Prospective, randomized and controlled study comparing the frequency of SLE and JSLE activity of patients with a stable dose of HCQ and patients with dose reduction of this drug and its correlation with the blood levels of its metabolites.

2. PRINCIPAL INVESTIGATOR:

ELOISA BONFA

Position/ Role: Full Professor of the Discipline of Rheumatology, Faculty of Medicine, HC-FMUSP.

Registration at Regional Council No. 42,708

HC-FMUSP Unit: Discipline of Rheumatology of HCFMUSP

3. RESEARCH RISK ASSESSMENT:

MINIMUM RISK ☐ MEDIUM RISK **X** LOW RISK ☐ INCREASED risk ☐

4. SEARCH DURATION: 12 months

INTRODUCTION: You are being invited to participate in this research because you have a rheumatologic disease (systemic lupus erythematosus) and are using hydroxychloroquine as a treatment for your disease. The information about the study is detailed in this document and will be explained by the researchers, who will answer any questions. We ask you to read this term carefully and feel free to ask any questions that arise to you about it.

STUDY PURPOSE: Hydroxychloroquine is used to treat various autoimmune rheumatologic diseases including systemic lupus erythematosus (SLE). Despite regular daily use of 1 tablet (400 mg) to control the inflammatory activity of the disease, each patient has a different level in the blood. It is important to know that the effectiveness of this drug depends on the drug blood levels. The aim of this research is to measure the level of hydroxychloroquine in your blood and saliva when you are taking this drug. What we want to know is whether this test that measure the blood level can identify patients who have a good response to the drug or not.

INCLUSION CRITERIA: Patients with systemic lupus erythematosus (SLE) who will experiences withdrawal of hydroxychloroquine may participate in this study. Your participation is voluntary and if you do not wish to participate, or want to leave the study, this will not change your follow-up in the Hospital at all. Only patients who agree to sign this document will be accepted in the study.

EXCLUSION CRITERIA: Patients with infection, liver disease, alcohol disease, dialysis, or using some drugs that interact with hydroxychloroquine (cimetidine, antiacids, digoxin, aminoglycosides, penicillin, neostigmine, pyridostigmine) may not participate in the study.

PROCEDURES: Upon entering the study, you will make a medical consultation and along with the blood tests that are normally done, an additional blood sample will be taken for the hydroxychloroquine dosage. You will be selected to use the normal dose of this medication (1 tablet) or a smaller dose (half) for 1 year. During the study, all participating patients will be evaluated at the entrance and after 3, 6 and 12 months to determine the effects of the medication. In each of these assessments, the patient will undergo medical consultation and blood test collection. You will also be asked to spit a little in a tube for saliva collection.

RISKS AND DISCOMFORTS: The blood test will be collected together with the other tests and a little pain or swelling may occur at the site of blood collection.

VOLUNTARY PARTICIPATION/ EXIT FROM THE STUDY: Your participation is completely voluntary, that is, you may decide whether or not to participate in this study and you are also free to leave the study at any time, without any prejudice or loss of your rights to follow-up and treatment in the Hospital. If you decide to participate, you must sign this informed consent (last sheet) and initial (make a small signature) on all other sheets. One way will be provided to you and the other will be saved by the researcher. If you decide not to participate in the study, or leave it, this decision will have no influence on your future medical care.

BENEFITS: The main benefit is whether the drug is doing a good control of the inflammation of your disease. There are no financial benefits for you or researchers. You will be informed of all test results.

CONFIDENTIALITY: This search is confidential and your personal data will not be disclosed in any event to others. The secrecy of the study will only be broken in cases where there is legal authorization to do so. The results of this study may be presented in congresses or in scientific publications, but their identity will always be preserved. The data collected in this study will be used only for this research.

COMMERCIAL INTERESTS: The study will be free of charge. Since there are no economic or financial interests on the part of participating institutions, you, your family or any of the researchers are not expected to receive any payment for participating in it.

MORE INFORMATION: This consent was approved by the Ethics, Teaching and Research Committee (institutional review board) of this institution. If you have additional questions regarding the survey or any other questions or symptoms, please contact:

Prof. Eloisa Bonfa, MD, Dr. Eduardo Ferreira Borba Neto, at the addresses and phone numbers below:

- Address: Faculdade de Medicina da USP Av. Dr. Arnaldo, No. 455 - 3rd floor, room 3150. Cerqueira César, São Paulo - SP. Zip code: 01246-903

- Phones: (+5511) 3061-7492 / (+5511) 3061-7490 (Secretary of the Rheumatology Division, Faculdade de Medicina da USP), (+5511) 2661-6105 (Outpatient Clinic of the Rheumatology Division, Hospital das Clinicas, Faculdade de Medicina da USP)

- Email: reumato@usp.br

If you have any considerations or doubts about the ethics of this research, please contact the Research Ethics Committee (REC) at the following address: Ovídio Pires de Campos Street, 225 - 5th floor. Phones: (+5511) 2661-7585, 2661-1548, and 2661-1549. E-mail: cappesq.adm@hc.fm.usp.br.

I believe I have been sufficiently informed about the information I have read or read to me, describing the **study "Prospective, randomized and controlled study comparing the frequency of SLE and JSLE activity of patients with a stable dose of HCQ and patients with dose reduction of this drug and its correlation with the blood** levels of its metabolites**"**. I argued with **Prof. Dr. Eloisa Bonfa on** my decision to participate in this study. They became clear to me what are the purposes of the study, the procedures to be performed, their discomforts and risks, the guarantees of confidentiality and permanent clarification. It was also clear that my participation is free of expenses and that I have guaranteed access to hospital treatment when necessary. I voluntarily agree to participate in this study and may withdraw my consent at any time, before or during it, without penalty or loss or loss of any benefit I may have acquired, or in my service on that Service.

_____

Patient/ legal representative signature Date: ___/____/_____

_____

Witness signature Date: ___/____/_____

For cases of patients under 18 years old, illiterate, semi-illiterate or with hearing or visual impairment.

(Only for the researcher)

I declare that I have appropriately and voluntarily obtained the Informed Consent of this patient or legal representative to participate in this study.

_____

Researcher in charge signature Date: ___/____/_____

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP FREE AND INFORMED CONSENT TERM

IDENTIFICATION DATA OF THE RESEARCH SUBJECT OR LEGAL GUARDIAN

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2. LEGAL GUARDIAN.....

NATURE (degree of kinship, tutor, healer, etc.):.....

ID No: ..... SEX: M ☐ F ☐

DATE OF BIRTH: ...../...../.....

Address:..... Nº: ..... Fit:.....

Neighborhood:..... City:.....

Zip code:..... PHONE: DDD (.....) .....

RESEARCH DATA

1. TITLE OF THE RESEARCH PROTOCOL:

PROJECT THEME: EVALUATION OF THE RELEVANCE OF BLOOD DRUG LEVELS USED IN AUTOIMMUNE RHEUMATOLOGICAL DISEASES IN THE MONITORING OF SAFETY / EFFECTIVENESS OF THERAPY, DISEASE ACTIVITY AND ADHERENCE TO TREATMENT.

SUB-PROJECT: TREATMENT EVALUATION OF CUTANEOUS LUPUS ERYTHEMATOSUS WITH THALIDOMIDE: CLINICAL, LABORATORY AND HISTOLOGICAL FACTORS ASSOCIATED WITH CLINICAL RESPONSE AND ADVERSE EVENTS.

2. MAIN RESEARCHER:

ELOISA BONFA

Position / Function: Full Professor of the Department of Rheumatology,

Faculdade de Medicina, HCFMUSP.

Registration with the Regional Council Nº: 42,708

HC-FMUSP Division: Discipline of Rheumatology, HCFMUSP

3. RESEARCH RISK ASSESSMENT:

MINIMUM RISK LOW RISK MEDIUM RISK HIGH RISK

4. RESEARCH DURATION: 12 months

INTRODUCTION: You are being invited to participate in this research because you have lupus erythematosus, which, at the moment, is causing skin inflammation, even though you are already receiving medication for lupus, such as prednisone and / or hydroxychloroquine and / or dapsone and / or immunosuppressive drugs (which lower immunity). The information about the study is detailed in this document and will be explained to you by the researchers, who will answer any questions. We ask you to read this term carefully and feel free to ask any questions that may arise from it.

INCLUSION CRITERIA: Adult patients with lupus erythematosus who, at the time of entry into the survey, present inflamed lesions on their skin and need treatment can participate in this study. Your participation is voluntary and, if you do not wish to participate, or want to leave the study, this will not change your follow-up at the Hospital in any way. Only patients who agree to sign this document will be accepted into the study. In addition, as Thalidomide is a teratogenic medication (i.e., it can cause fetal malformations), only the following patients will be included: 1. Adult men, who agree to use condoms in all sexual relations during the study period and up to one month after stopping medication (13 months in total), even if they have already had a vasectomy. Note: condoms will be provided free of charge by the researchers. 2. Women who have been □in menopause□ for more than a year (and we will order blood tests to confirm □menopause□), or who are sure they have had their tubes sterilized.

EXCLUSION CRITERIA: Will not be able to participate in the study: 1. Any woman who is at risk of getting pregnant, even if she is taking contraceptive medication or using an IUD. 2. Male patients who do not agree to use condoms as explained above. 3. Patients with a history of peripheral neuropathy (disease that affects the nerves of the legs and arms), thrombosis, pulmonary embolism or alcoholism.

PROCEDURES TO BE FOLLOWED: Upon entering the study, each patient must collect blood tests and undergo a medical consultation. Next, patients will be subjected to two skin biopsies, one in the area affected (inflamed) by the disease and the other in the skin of the thigh (not inflamed). Finally, an exam called Electroneuromyography will be performed, which serves to study the functioning of the nerves in the legs and arms (in this exam, small electrodes are placed in the arms and legs, to see if the nerves are working properly, lasting about half an hour). Skin biopsies are performed under local anesthesia, and a small piece (about 6 millimeters) is removed for examination. If there is no contraindication (alteration of nerves) in these evaluations, we will start treatment with Thalidomide orally at the dose of 1 tablet of 100 mg once daily. Note: You will keep taking your current medications for lupus. The dose of thalidomide and prednisone will be progressively decreased if the skin lesions improve. During the study, all participating patients will be evaluated periodically to determine the effects of the medication and possible side reactions (which are explained below). The first reevaluation should take place within two weeks, the second in 1 month and, thereafter, every 3 months, until completing 1 year of follow-up. In each of these assessments, the patient will undergo medical consultation and blood test collection. You will also be asked to spit in a test tube to collect a saliva sample. After 6 months of follow-up, patients should undergo a new skin biopsy of the leg and a second Electroneuromyography. Finally, after completing the 12 months of the study, a third Electroneuromyography will be performed. Note: If there is no clinical response within 2 months of using thalidomide, this medication will be suspended (you will no longer participate in this research)

and patient follow-up will be continued according to the routine of the Rheumatology and Dermatology Divisions of HCFMUSP.

RISKS AND DISCOMFORT: Thalidomide is considered a very effective medication for the treatment of skin lesions caused by lupus, which has been used for many years in the treatment of this disease. Despite this, some patients may develop side effects with the use of this medication, with peripheral neuropathy being one of the most common. Pain, tingling and / or loss of sensation in legs and arms characterize this adverse event, which can occur in about 25% of patients. When this happens, treatment with Thalidomide should be stopped as soon as possible, as this problem may be irreversible. For this reason, you will be reassessed frequently by the researching doctor and will also perform Electroneuromyography periodically and you can also contact us on the phones below. If you develop symptoms or signs of neuropathy on this exam, we will immediately withdrawal

thalidomide and you will continue to be followed up in the lupus outpatient clinic and medications will be used as per the routine of that clinic. In addition, to reduce the possible side effects, we will use low doses of the medication (maximum 1 tablet of 100 mg daily) (and this dose will be reduced, as soon as skin lesions are better, to half a tablet per day and then for a quarter of a pill a day) and for a maximum of 12 months (as peripheral neuropathy, when it appears, is usually after 1 year of Thalidomide`s treatment). Other possible side effects are: drowsiness, constipation, headache, bloating, dizziness, increased appetite, nausea, itching and weight gain. To reduce sleepiness, thalidomide should be taken at night. Skin biopsies and Electroneuromyography can also cause some pain or discomfort.

VOLUNTARY PARTICIPATION / STUDY EXIT: Your participation is completely voluntary, i.e., you can decide to participate or not in this study and you are also free to leave the study at any time, without any loss or loss of your follow-up and treatment rights at the Hospital. If you decide to participate, you must sign this informed consent (last sheet) and initials (make a small signature) on all other sheets. One copy will be provided to you and the researcher will keep the other. If you decide not to participate in or leave the study, that decision will have no influence on your future medical care.

BENEFITS: As already mentioned above, thalidomide is a very effective medication in the treatment of skin lesions caused by lupus erythematosus. Therefore, the main benefit will be the possible improvement of the lesions on your skin with the use of this medicine. There are no financial benefits either for you or for the researchers. You will be informed of all test results.

CONFIDENTIALITY: This survey is confidential and your personal data will not be revealed, under any circumstances, to other people. The confidentiality of the study will only be broken in cases where there is legal permission to do so. The results of the study may be presented at congresses or scientific publications, but your identity will always be preserved. The data collected in this study will be used only for this research.

COMMERCIAL INTERESTS: The study will be free of charge. As there are no economic or financial interests on the part of the participating institutions, you, your family or any of the researchers are not expected to receive any payment for participating in it.

MORE INFORMATION: This consent was approved by the Ethics, Teaching and Research Committee (institutional review board) of this institution. If you have additional questions regarding the survey or any other questions or symptoms, please contact:

Prof. Eloisa Bonfa, MD; Emily Figueiredo V. Neves, MD or Sandra G. Pasoto, MD at

the addresses and phone numbers below:

- Address: Faculdade de Medicina da USP Av. Dr. Arnaldo, No. 455 - 3rd floor, room 3150. Cerqueira César, São

Paulo - SP. Zip code: 01246-903

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I believe I have been sufficiently informed about the report that I have read or that have been read to me, describing the study **"TREATMENT EVALUATION OF CUTANEOUS LUPUS ERYTHEMATOSUS WITH THALIDOMIDE: CLINICAL, LABORATORY AND HISTOLOGICAL FACTORS ASSOCIATED WITH CLINICAL RESPONSE AND ADVERSE EVENTS"**. I discussed with Prof Eloisa Bonfa, MD about my decision to participate in this study. It became clear to me what the purposes of the study are, the procedures

to be performed, their discomforts and risks, the guarantees of confidentiality and permanent clarifications. It was also clear that my participation is free of charge and that I am guaranteed access to hospital treatment when necessary. I voluntarily agree to participate in this study and I will be able to withdraw my consent at any time, before or during the same, without penalties or prejudice or loss of any benefit that I may have acquired, or in my follow-up in that Service.

_____

Patient/ legal representative signature Date: ___/____/_____

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Witness signature Date: ___/____/_____

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I declare that I have appropriately and voluntarily obtained the Informed Consent of this patient or legal representative to participate in this study.

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Researcher in charge signature Date: ___/____/_____