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PSORIATICUM: Topical Hypericum Perforatum for Moderate Plaque Psoriasis: Study Protocol for a Randomized Controlled Trial

Monica Estrada[1], Ruth E Chavez-Nomberto[2], Ana Paula Tsuneto, Andre Saul Crestani[3], Andres Moreno, Carlos Takahiro Chone[4], Danieli Kimura[5], Davi Egete Gaino, David Leonardo Flores, Erivelton de Azevedo Lopes[6], Sekinah Bola-Oyebamiji[7], Habiba Ibrahim Abdullah[8], Haripriya Andamala, Jacob Eli García Torres[9], Jimena Vizarreta[10], Joaquín Díaz-Schmidt[11], Levi Higino Jales Neto[12], Michael Olusegun Akodu, Paula María Fernández González, Rodrigo Paredes, Santiago Sucre[13], Francisca Lopez Miguez, Yuri Costa Farago Fernandes, Luis Fernando López[14*]

[1] Universidad Francisco Marroquín, Guatemala; [2] Hospital Nacional Edgardo Rebagliati Martins, Perú; [3] Pontificia Catholic University of Parana, Brazil; [4] University of Campinas, Brazil; [5] Irmandade Santa Casa de Misericórdia de São Paulo, Brazil; [6] Albert Einstein Israelit Hospital, Brazil; [7] Osun State University, Nigeria; [8] University of Abuja, Nigeria; [9] Universidad Nacional Autónoma de México, México; [10] Universidad de San Martin de Porres, Peru; [11] Clínica Alemana de Santiago, Chile; [12] Sao Camilo Hospital, Brazil; [13] Universidad Central de Venezuela, Venezuela; [14] Pontificia Universidad Católica Madre y Maestra, Dominican Republic.

Abstract

Introduction: *Psoriasis is an autoimmune chronic inflammatory disorder in which an increased amount of Tumor Necrosis Factor Alpha (TNF-α) leads to the formation of psoriatic plaques. Hypericum perforatum (HP) is a flowering plant used as an herbal medication due to its antimicrobial, wound-healing, and anti-inflammatory properties. Pilot studies have reported its ability to decrease the levels of TNF-α and severity of psoriatic plaques in moderate forms of psoriasis with fewer side effects and lower costs compared to standard treatment. More extensive studies are needed to confirm this.*

Objective: *To assess the effectiveness of topical HP in decreasing the mean total PASI score at the end of 12 weeks in patients with moderate plaque psoriasis.*

Methods: *PSORIATICUM is a phase II, single-center, two-arm parallel, double-blinded randomized clinical trial that has the purpose of evaluating the efficacy of HP versus a control vehicle based on the decrease of the PASI score. The primary outcome is the total PASI score in the treatment group, compared to the control group at the end of the 12 weeks of testing. Normality will be evaluated using Kolmogorv-Smirnov, having the statistical significance of the findings tested using a two-tail Student's T test for independent means or Mann-Whitney-Wilcoxon test. The secondary outcomes include the mean PASI change at weeks 4 and 8.*

Discussion: *PSORIATICUM will provide information about the usefulness of Hypericum perforatum to treat psoriasis, allowing for future trials to study a safe and accessible alternative treatment for the condition.*

Introduction

Background

Psoriasis is an autoimmune chronic inflammatory disorder that affects around 125 million people worldwide (Melnikova, 2009). Its prevalence varies according to age, ethnicity, and geographic region (Langley et al., 2005). Psoriasis imposes a considerable economic burden on US citizens ($35.2 billion) and affects their quality of life (Vanderpuye-Orgle et al., 2015; Solmaz et al., 2021).

Mechanisms and Existing Knowledge

Tumor necrosis factor alpha (TNFα) plays a role in psoriasis physiopathology. It increases the microvas-

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cular permeability and angiogenesis. It also induces keratinocyte proliferation and prevents apoptosis, resulting in the silvery plaques characteristic of psoriasis (Gottlieb et al., 2003; Markham et al., 2006).

About 80% of patients in European countries and the US have mild disease, 5 to 13% moderate (Psoriasis Area Severity Index (PASI) $\leq$10), and 9% severe (PASI >10) (Sanclemente et al., 2022). For the non-severe forms, topical therapy such as corticosteroids, vitamin D and A derivatives, and anthralin provide high efficacy but with poor adherence, possibly due to side effects (SE) (Menter et al., 2009; Devaux et al., 2012).

Hypericum perforatum (HP), also known as Saint John's Wort (SJW), is a flowering plant that has been used as herbal medication due to its antimicrobial, anti-depressant wound-healing and anti-inflammatory properties, which also have some interaction with other drugs, as it acts as an inducer on the cytochrome P450 (Peterson & Nguyen, 2022; Uva et al., 2012; Russo et al., 2014; Wölfle et al., 2014; Zhang et al., 2021; Najafizadeh et al., 2012). HP ointment applied twice daily for four weeks significantly reduced the PASI score index in a pilot study done with ten mild psoriasis patients (Najafizadeh et al., 2012). Mansouri et al. studied 20 patients and showed improved PASI scores and decreased TNF-α concentration in epidermis, endothelial cells, and dendritic cells in treated cells with HP (Mansouri et al., 2017).

Need for a Trial

The mainstream psoriasis treatment is topical corticosteroids. Steroids are associated with side effects such as skin atrophy, telangiectasia, striae, and hypothalamic-pituitary axis suppression. (Armstrong & Read, 2020). It is also characterized by poor adherence (Menter et al., 2009; Devaux et al., 2012). There is a need for research on newer topical treatments with fewer side effects and enough potency to generate a clinical response.

Choice of Comparators

There needs to be more clinical data about the effect of topical HP in non-severe psoriasis. The active component of HP ointment will be compared to a usual ointment-based topical moisturizer.

Over-the-counter moisturizers have a 15% to 47% response rate compared to topical corticosteroids (Uva et al., 2012). The effectiveness of adding an HP component on the decrease of the mean PASI score compared to using a standardized moisturizer will be evaluated.

Research Question and Hypotheses

The trial will evaluate the decrease in the mean total PASI score of psoriatic plaques with Hypericum perforatum-based ointment compared to moisturizer after 12 weeks of treatment in adult patients with moderate plaque psoriasis (PASI score > five and $\leq$10).

Significance /Impact of the Study

HP is a promising alternative drug to treat moderate psoriasis, with fewer side effects and lower costs than standard treatment. Its broad current use as a non-prescription treatment for several skin diseases supports its safety (Wölfle et al., 2014).

Study Design

PSORIATICUM is a phase II, single-center, two-arm parallel, double-blinded, randomized clinical trial proposed to evaluate the efficacy of HP against a control vehicle ointment in adult patients diagnosed with moderate plaque psoriasis during a follow-up period of 12 weeks.

Study Setting

The study will be performed in the Dermatology Clinic of Toronto Western Hospital, an academic tertiary referral level affiliated with the University of Toronto. This center is located in the City of Toronto, the capital of Ontario, Canada (Dermatology Clinic, n.d.).

Toronto Western Hospital receives a large population of patients and has been involved in scientific research in each of its 13 program elements in different fields of medicine (Dermatology Clinic, n.d.). Therefore, this center is suitable due to its location in a city with a dense population in Canada, its experience in scientific research, and the high prevalence of psoriasis in Canada (Damiani et al., 2021). It will allow us to recruit patients with the required characteristics efficiently and conduct the study.

Eligibility Criteria

To be eligible, patients must be able to provide written informed consent, be 18 to 65 years old, and have moderate plaque psoriasis for at least six months at baseline. Exclusion criteria are patients with non-plaque forms or severe psoriasis (PASI score >10), other skin conditions, smoking, presence

of comorbidities (including diabetes mellitus, cancer, immunosuppression, active infection, peripheral vascular disease, other immunosuppressive or autoimmune diseases), postmenopausal women without systemic hormone therapy, pregnancy and use of concomitant treatments, such as the use of any anti-psoriatic systemic or topical treatment, corticosteroids, and immunosuppressive therapy (Bissonnette et al., 2012; Lebwohl et al., 2020).

Recruitment Strategy

A mixed recruitment strategy will be applied: broad-based and targeted enrollment strategies. The trial will be advertised online via Google Ads and through posters and leaflets placed on-site and in referral centers. Invitation letters will be sent to physicians in referral centers. Subsequently, an initial eligibility screening will be performed over the phone. Prospective candidates will be evaluated, and if eligible, they will sign an informed consent. All patients will be recruited consecutively.

Interventions

After a washout period of 4 weeks, patients will be instructed to refrain from using any topical medication for psoriasis. They will be instructed to apply a thin layer of the ointment twice daily to cover psoriatic lesions completely. They will choose the application time they prefer and apply the ointment at the same time each day for 12 weeks. Subjects will be instructed to record each application in a daily diary. These data will be used to estimate adherence to the trial.

The active ointment will be prepared from an extract of H. perforatum L (5% wt/wt), vaseline (84% wt/wt), propylene glycol (10% wt/wt), and avicel (1% wt/wt). The control ointment will have the same color, odor, skin sensation, and percentages of propylene glycol, vaseline, and avicel as the active treatment. The formulations will be packed in airtight bottles and undergo stability tests (Najafizadeh et al., 2012; Mansouri et al., 2017).

Half of the bottles will be filled with the HP formulation, and the other half with the control formulation.

Modification / Discontinuation

A subject is obliged to discontinue their participation in this study if any of the following conditions are met:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study (including pregnancy).
- The subject withdraws consent to continue the study's proposed treatment.
- The subject experiences a severe adverse reaction (as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0, 2017) as a consequence of the treatment that limits their participation as determined by the PI and/or Co-Investigators (the adverse event (AE) must be reported).
- The subject must undergo a medical treatment that prevents them from continuing the study treatment.
- The subject experiences a medical emergency that unblinds the treatment assignment or cannot comply with the protocol.
- At the discretion of the investigators.
- The subject develops severe psoriasis during the study.

Subjects who withdraw or discontinue treatment are encouraged to remain in the study for follow-up appointments and protocol-required tests.

Randomization and Blinding

Patients will be randomized to the HP or control group with a 1:1 ratio allocation per computer-generated randomization with random size blocks of four and six. The allocation sequence will be computer generated using REDCap web application version 12.4.0, and the size of the blocks will not be revealed.

To ensure allocation concealment, the sequence will be computer-generated and distributed through sealed opaque envelopes, only opened when a subject is enrolled. The final allocation sequence will only be known to the pharmacist handling and distributing the ointments. The bottles of both ointments will be delivered with a code traceable to the patient's randomized assigned group of treatment.

To maintain allocation concealment, the person who will generate the randomization sequence will be different from the one working with the allocation. These two persons will also be independent of the investigators and statisticians. A study coordinator will check all envelopes are sealed and not tempered.

Once the patients are enrolled, the clinician-researcher responsible for the study will request the subject's corresponding envelope. The pharmacist will then deliver the treatment to the physician based on the randomization code number assigned to each participant. Physicians and patients will be blinded by using a control vehicle.

Code breaking may be applied in the event of a medical emergency, serious AE, or severe medical

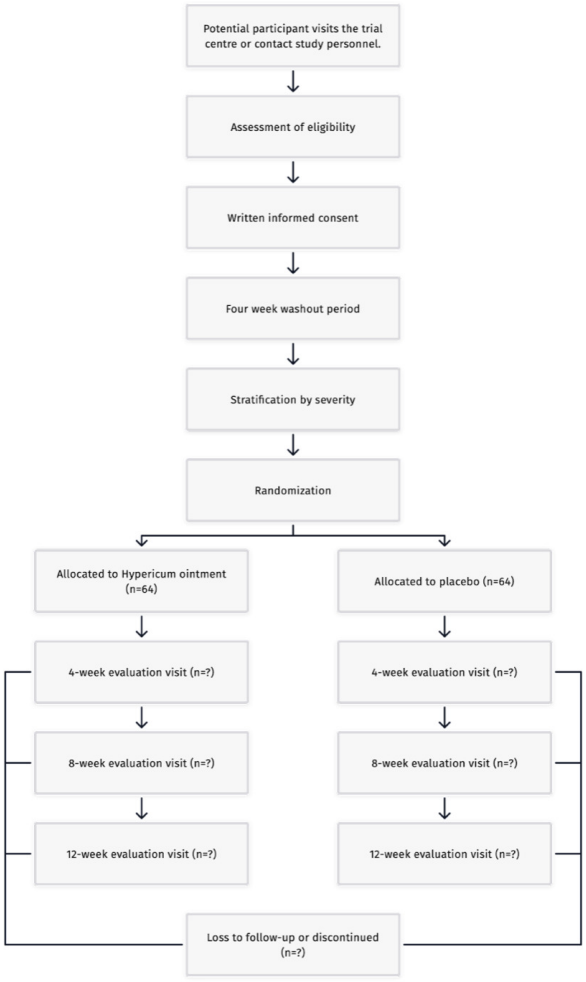

Figure 1: *Timeline.*

condition that threatens life, in which knowledge of participants' allocation is necessary for the appropriate management or welfare of the subject. In this scenario, the investigator should contact the principal researcher to discuss options before proceeding with unblinding unless this would delay further participant management.

A case report form (CRF) should be completed, stating the date and reason for unblinding, and the unblinded subject will be removed from the trial but still included in the analysis. Serious AEs will be reported to regulatory agencies following local regulations.

Adherence

Patients will be instructed to apply the ointment every 12 hours daily, maintaining the same schedule. They will be instructed to keep a diary to record the applications to estimate adherence. At every visit, evaluators will ask about adherence and challenges patients might face to provide strategies to help them. The ointment container will be inspected on each visit to confirm adherence.

Travel expenses will be reimbursed for patients from out of town, and accommodation will be provided to promote follow-up and decrease the drop-out rate.

Timeline

The timeline of the study is shown in Figure 1.

Sample Size Calculation

The sample size was calculated based on the primary hypothesis. In a pilot study, Najafizadeh et al. demonstrated a statistically significant reduction in disease activity with topical HP in ten patients with psoriasis (20 psoriatic plaques) (Najafizadeh et al., 2012). Erythema, scaling, and thickness scores decreased consistently with an aggregate mean reduction of 1.5 on a 3-point scale (50%) compared to an aggregate mean reduction of approximately 0.4 on a 3-point scale (13%) in the control arm. The mean PASI score of the sample was 8.7 (SD 3.8). PASI scores for both arms before and after treatment were not reported. An exploratory longitudinal study by Ljossa et al. found a spontaneous mean PASI score change of –1.4 (SD 4.0) at three months follow-up from a mean baseline of 5.5 (SD 4.9), approximately a 25% decrease (Ljosaa et al., 2013).

Even though a 75% reduction in PASI score (PASI 75) is considered the benchmark in psoriasis clinical trials, Carlin et al. state that some researchers consider it too stringent. In contrast, a decrease of 50% in PASI score (PASI 50) has been considered a clinically significant reduction with demonstrated improvements in quality of life measurements (Carlin et al., 2004). Because of this, the reported 50% effect size in the intervention arm of the trial by Najafizadeh et al. was noted as an interesting result.

Considering the results of the studies by Najafizadeh et al. and Ljossa et al., the difference of approximately 37% found in the pilot study plus the reported spontaneous variability of roughly 25% in PASI scores at 12 weeks is intrinsic to the natural course of the disease and response to the emollients. The estimation of the sample size calculation was based on this information.

To detect a clinical improvement as evaluated by a decrease in the mean PASI score from baseline to 12 weeks of exposure to the intervention, the following parameters were considered: a hypothetical baseline PASI score similar to that found in the pilot study (PASI = 8.7); a standard deviation of 4.0 (based on findings of the pilot study where SD was 3.8, and maybe it was underestimated compared to the other

studies) with a 25% response in the control arm owing to the effect of moisturizer on the lesion (mean of 6.5); and a conservative difference in response of 25% between groups leading to a 50% decrease in the treatment arm (mean of 4.3). Considering a 2-sided 0.05 significance level and 80% power with equal allocation, the estimated sample size is 53 per group (N = 106). Assuming a 20% loss to follow-up, the adjusted sample size is N=128 (20% of 106), with 64 patients per group.

Outcomes

The primary outcome is the mean decrease in total PASI score from baseline to the end of 12 weeks. The secondary outcomes include the mean PASI change at weeks 4 and 8, the percentage of patients achieving PASI 50 and 75 at the end of 12 weeks, mean change in the Dermatology Quality of Life Index (DLQI: a 10-item self-administered questionnaire that provides a method of scoring the impact of skin disease on quality of life) at the end of 12 weeks, adherence and drop-out rates. After the end of treatment, all participants will have the option to be evaluated for four more weeks to check for the presence of a rebound.

The incidence, type, and severity of AEs will also be reviewed as exploratory results. An AE is "an unexpected medical problem that happens during treatment with a drug or other therapy. AEs may be mild, moderate, or severe and may be caused by something other than the drug or therapy. Also called AE" (NCI Dictionary of Cancer Terms, 2019). All AEs will be classified as described in section 2.6. Frequency, severity, and causal relationship of AEs will be tabulated by system organ class (SOC) and preferred term according to the current version of the MedDRA.

Patients will be instructed to report any AE using a semi-structured questionnaire, which a dermatologist will assess. The staff responsible for investigating, documenting, and reporting AEs must know group allocation.

Data Management

Data will be collected via electronic Case Report Forms (eCRF) by the evaluators or self-reported by patients when needed for quality-of-life questionnaires. Different eCRFs will be used for evaluators and patients at the study site. The original eCRFs will be kept in a file at the original site. They will also be sent to the Coordinating Center to be entered electronically into the database using a data capture system (OpenClinica). To detect errors and missing data, a subset of Target eCRFs will be requested later for quality control. These will be reported to the Data Coordinating Center to be checked and make corrections when necessary.

The study will have a Data Monitoring Committee (DMC) independent from the sponsors and investigators. It will be composed of five independent members with different backgrounds (clinician, clinical trial expert, biostatistician, bioethicist, and patient advocate). The DMC will ensure the study participants' safety and the data's validity and integrity. Also, make recommendations to sponsors and investigators concerning the continuation, termination, or other modifications of the study based on the observed beneficial or adverse effects of the study and the interim analysis results.

Interim Analysis

An interim analysis will be conducted when 50% of the patients have been enrolled. Efficacy and safety will be evaluated using the Pocock approach. The significance level for the interim and final analysis will be set at 0.025. The DMC will assess the results, and investigators cannot access the analysis results. The evaluators will monitor safety through physical exams and responses to general open questions made to the participants. AEs will be classified according to the same parameters aforementioned in section 2.6.

Statistical Analysis for Primary and Secondary Outcomes

The primary outcome is the mean total PASI score of participants in the treatment group compared to the control group at the end of 12 weeks of testing. After assessing normality with a histogram and the Kolmogorv-Smirnov test, the findings' statistical significance will be tested using a two-tailed Student's T test for independent means or the Mann-Whitney-Wilcoxon test. Secondary analysis to adjust for the severity variable (the baseline PASI score) will be performed through linear regression. Data will be reported as frequencies and percentages for categorical data and means and SD for quantitative data, as appropriate.

Secondary outcomes include the change in the mean value of PASI at weeks 4 and 8, the percentage of patients that achieved PASI 50 and 75, the mean change in the Dermatology Quality of Life Index, and dropout rates at the end of the 12 weeks. A chi-squared test will be used for binary outcomes. A linear mixed model for repeated PASI measures at weeks 4 and 8 will be used to analyze the mean change through time.

The percentage of dropout rates within each arm

can be compared and may also reflect patients' adherence due to side effects. PASI score will be assessed at or before patients drop out to evaluate if dropping out occurred due to dramatic changes in the disease activity.

All statistical calculations will be made with STATA 17.0 Basic Edition. (StataCorp 4905 Lakeway Drive, College Station, Texas 77845 USA)

Superiority will be tested using the intention-to-treat principle to preserve the generalizability of results by reflecting the reality of clinical practice. Multiple imputations will be used to account for missing data.

Discussion

PSORIATICUM is a phase II, single-center, two-arm parallel, double-blinded, randomized clinical trial. The results of this trial could broaden the knowledge and evidence of the efficacy and safety of topical HP as a treatment of psoriasis in a larger population compared to previous studies. The randomization and blinding strategies in the design will reduce the introduction of bias. Continuous outcome (mean total PASI score) will increase the study's internal validity, allowing the collection of vast information and data for a more robust and powerful statistical analysis. The study will also explore secondary outcomes that could help provide evidence and data to develop future studies.

The decision to use a mean total decrease in PASI score as the primary outcome was based on the fact that the only previous studies focused on the topic were pilot clinical trials. Additionally, PSORIATICUM intends to provide more information on efficacy before testing effectiveness; therefore, a continuous outcome was considered a better alternative. It was decided to compare it against a control vehicle and dispense a DMC and interim analysis because the trial has a short duration. As plaque psoriasis is not considered life-threatening, the control vehicle will also slightly reduce the plaques (Mansouri et al., 2017; Najafizadeh et al., 2012). Additionally, there are criteria for discontinuing the active treatment in the case of AEs, which will be documented and treated accordingly.

Active treatment could be inefficient or even worsen the condition; because of this, a 2-sided significance level will be used in the statistical analysis. In either of the two scenarios, the result from the trial would continue to be relevant since the prosecution intends to cover a knowledge gap: finding a safer, more efficient, and cost-effective alternative treatment for plaque psoriasis.

H. perforatum promises to be an alternative for the topical treatment of plaque psoriasis. Determining safety and efficacy as an ointment could decrease the financial burden of treatment and improve the quality of life of patients with psoriasis. Previous clinical trials showed promising results in small samples. Conducting the PSORIATICUM trial will broaden the knowledge and evidence on the safety and efficacy of HP as a topical treatment. A positive result would mean the possible confirmation of HP as a new, safe, efficient treatment to be further investigated. A negative one would help optimize time and costs by moving on to study other alternatives.

Limitations of the PSORIATICUM trial include a decrease in the study's external validity because the results will not be measured through the traditionally used PASI 50 and PASI 75 scores. These outcomes focus on the considered significant clinical results of the treatment. Despite positive results, more studies will be needed to assess the clinical significance of the intervention's effect.

Author Contributions

All authors contributed equally to the conceptualization, methodology, software, validation, investigation, writing, reviewing, and editing of this article. Additionally, all the authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

E. De Azevedo Lopes reports receiving consulting fees for preparing events for GlaxoSmithKline (GSK) Pharmaceutical Industry Company.

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