The Relation Amongst Substance P and Tackling Atopic Dermatitis

Group 1: Somatosensation, Pain and Itch

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Introduction

Atopic dermatitis, also known as eczema, is a chronic inflammatory skin condition that affects millions of people worldwide. Affecting up to 20% of children and 10% of adults (Silverberg, 2019), it not only compromises physical comfort but also impact a patient's sleep, concentration and overall, their quality of life, with one of its most frustrating and common symptoms being intense itching. While there are many treatments options, such as topical steroids and biologics, they do not always provide long-term relief and effective results. Some treatments also are accompanied by side effects, high costs or the need to frequently visit a doctor. Due to these challenges, researchers are looking into alternative and better approaches, including targeting Substance *P*, which is a neuropeptide involved in transmitting pain and itchy signals in the nervous system.

Recent evidence has highlighted the role of Substance *P* (SP) in exacerbating itch and inflammation in skin diseases, including AD. SP is released from sensory neurons and interacts with neurokinin-1 (NK-1) receptors on immune and skin cells, promoting mast cell degranulation, cytokine release, and increased vascular permeability (Steinhoff et al., 2014). These effects contributed to both sensory experience of itch and the downstream inflammatory cascade seen in Atopic Dermatitis.

In our proposed study, we will be using Aprepitant, an FDA-approved NK-1R antagonist originally developed to prevent chemotherapy-induced nausea. Aprepitant works by blocking Substance P from binding to NK-1 receptors, thereby potentially reducing both itch and inflammation. Several studies support the use of Aprepitant for this purpose. For example, Ständer et al. (2010) conducted an open-label trial in which Aprepitant significantly reduced

chronic pruritus, including in patients with atopic dermatitis. Fostini et al. (2020) further reviewed its antipruritic potential and highlighted the relevance of NK-1R antagonists in dermatology.

Our research question addresses: *What is the relation between Substance P and atopic dermatitis and how could it be incorporated as a form of oral treatment to tackle the condition?*

The research question was proposed to identify a sufficient accompanied with permanent treatment for atopic dermatitis, as the condition has a severe impact on the quality of life for numerous individuals. Currently, the treatments affiliated with atopic dermatitis provide minor temporary relief and often come with either immense side effects or limitations. Substance *P* is a neuropeptide that is associated with inflammation and itch signaling, which are the two main symptoms of atopic dermatitis. Our group wanted to examine the specific role of Substance *P* within atopic dermatitis and to research how it can be used as an effective treatment orally.

We hypothesize that taking an oral Substance *P* antagonist will significantly reduce itch levels and inflammation in individuals with atopic dermatitis compared to those who do not receive the medication. There are some alternative possibilities to consider, including no significant effect, which means that if the treatment does not reduce itch or inflammation, targeting Substance P alone is not enough to manage the eczema symptoms. On the other hand, there may be no significant improvements, which suggests that blocking Substance *P* has unintended effects on the skin or in the immune system. By testing these possibilities, we aim to better understand the role of Substance *P* in eczema and determine whether this approach is a viable and successful treatment option.

Given this support, we expect to find that patients treated with an NK-1 antagonist will show lower scoring across behavioral and physiological scale of atopic dermatitis from reduced

subjective itch ratings, decreased levels of inflammatory cytokines and improved skin barrier function. We propose to experimentally test this using a double-blind, placebo-controlled human study.

Methods

We propose a 4-week double-blind randomized controlled trial to assess the impact of oral NK-1R antagonist on AD symptomatology.

Variables

All groups will be measured on their itch levels before and after as the behavioral component. All groups will be measured from plasma SP levels post-treatment as the physiological component. To compare the neural network changes, present within the SP levels, an fMRI apparatus will be utilized. Before beginning any procedures, all participants will complete SCORAD, PHQ-9, and DLQI. The SP levels will be measured from accumulating blood samples through ELISA (enzyme-linked immunosorbent assay). The variables affiliated with the experiment are as follows:

Independent Variable

The experiment attains two groups- the treatment group adjoined with the placebo group. The treatment group will receive an 80mg oral tablet of a NK-1 receptor antagonist known to inhibit the effects of Substance P (Aprepitant-like treatment). The placebo group will receive an inert substance (sugar pill) with no pharmacological effect for comparison reasons.

Dependent Variable

The particular variable aimed to be measured is the contrast amongst itch levels before and after the treatment. There are particular examinations that the participants will go forth in doing, which includes:

1). **SCORAD- Itch Severity:**

This is measured through using a numerical rating scale ranging from 0 (no itch) to 10 (worst imaginable itch). Participants will report their average itch intensity over the past 24 hours at baseline, day 0 and post-treatment, day 28.

2). **DLQI and Eczema Severity:**

The eczema severity is assessed using the Scoring Atopic Dermatitis index, which combines objective symptoms and subjective symptoms. Higher scores tend to indicate severe eczema whilst lower scores will depict less intense eczema. The DLQI (Dermatology Life Quality Index) aims to assess the influence of atopic dermatitis on the participant's quality of life.

3). **PHQI-9 - Depression:**

The PHQI-9 (Patient Health Questionnaire-9) evaluation aims to examine any depressive symptoms that have arisen due to the eczema.

4). **ELISA- TSerum IL-31 Levels (SP Plasma):**

IL-31 is a pro-inflammatory cytokine associated with pruritus and eczema severity. Blood samples will be collected at baseline and post-treatment to quantify IL-31 levels (pg/mL) via enzyme-linked immunosorbent assay (ELISA). Evaluation of NK-1 Substance *P* will also be extracted from blood samples, as it is associated with the pain and itch sensation component, producing mast cells. The fMRI apparatus will be incorporated to evaluate the samples.

Control Variable:

To remain a controlled study, participants will be balanced across groups. In addition to this, the incorporation of a control group (placebo treatment) will be initiated to compare results.

Subjects

The subjects that will be mainly focused on would include adolescents (particularly within the age ranges of 15-24) accompanied with children (specifically within the age ranges of 6-14) with mild to severe eczema. The study will collaborate with clinical research sites that have been recognized for executing atopic dermatitis treatment trials-preferably the "ForCare Clinical Research" facility in Florida- and recruit the participants diagnosed with atopic dermatitis from local dermatology clinics. The sample size for all three groups would be 180 individuals, of which sixty would be distributed within each group.

The groups will have an equal distribution of 30 males and 30 females to refrain from any gender bias as well as to collect reliable data. In addition to this, we aim to assess potential divergent symptoms associated with gender to recognize how effective the treatment is, side effect profiles, and any gender-specific responses evoked upon taking the Substance *P* antagonist. Prior studies have shown that gender differences in adult patients diagnosed with atopic dermatitis have mainly occurred due to population variations; however, have depicted the suboptimal treatment approaches amongst female patients/participants. A study conducted in 2023 by Marani et.al aimed to discover gender differences within adult atopic dermatitis and had reported that there was also a minor difference in treatment as the male participants received an increase of methotrexate; to which the males had therefore reported increased high rates of hypertriglyceridemia and hypertension. With this being said, it is crucial to ensure that there is an

equal distribution of males and females to therefore allow for accurate comparisons and eventually provide a consistent treatment.

In terms of demographics, the participants will be affiliated with cultural backgrounds including Hispanic/Latino populations (25%), Asian populations (25%), White populations (25%), and Black populations (25%). The comparison group consists of 60 adolescents adjoined with children with no presentation of eczema that will be incorporated to thus examine how effective the oral Substance *P* antagonist treatment is.

Exclusion Criteria

Participants that have been diagnosed with atopic dermatitis and attain symptoms of intense itching will be considered for the study. Participants that attain other skin conditions- which includes, but is not limited to, psoriasis, chronic urticaria, neurodermatitis, etc.- will be excluded from the study to avoid any interference with the assessment of atopic dermatitis. Participants that acquire allergies or hypersensitivity to Substance *P* antagonists will not be considered for the study. Pregnant and breastfeeding individuals will be excluded from the study due to the potential risks. Lastly, participants that are already diagnosed with severe depression or neurological disorders will be excluded to ensure the accuracy of behavioral evaluations.

Procedure

Phase I: Preliminaries

Participants diagnosed with atopic dermatitis will be recruited from local dermatology clinics throughout Florida. Recruitment tactics include outreach through clinic networks, referrals from physicians, and electronic health record screenings. All participants will be provided with an informed consent form that displays the aim of the experiment, detailed information on the experimental procedure, potential risks and benefits, adjoined with the

confirmation/nature of participation. Participants will be asked to read completely through the form and to sign if participation is applicable. Copies of the form will be evoked to therefore provide participants with records of their participation. For participants that are under the age of 18, a legal parent or guardian will be responsible for not only signing the informed consent form, but to also be present within the stages of the experiment. The legal guardian or parent is also responsible for explaining the basis of the experiment to the child. Participants will also be asked to give information pertaining to their medical records and current treatment taken for the condition.

Phase II: Testing/Questionnaire and Treatment Sessions

The experiment will take place at the "ForCare Clinical Research" located in Tampa, in which participants will continuously attend the clinic for a duration of 4 weeks. Following consent, and before beginning any procedures, all participants will complete SCORAD (Scoring Atopic Dermatitis)— five dimensions are degree (how intense the itch feels), duration (how long it lasts), direction (whether it is spreading or staying the same), disability (how much it interferes with daily activities) and distribution (where in the body does it occur), that will be our behavioral component. The SCORAD index acquires three main components- the severity of clinical signs, the participant-perceived experiences of the participant, and the scope of dermatologic impact. The extent of atopic dermatitis will be assessed through the utilization of the "rules of nine," where essentially an estimated percentage of the distribution of dermatologic involvement present across the body will be evoked (skin inflammation, rashes, and itching). Participants must rate the subjective symptoms (itching, sleep disturbance, skin inflammation, etc.) experienced within the past week on a visual analog scale from 0 to 10.

After the completion of SCORAD, participants will then be asked to complete a PHQ-9 (Patient Health Questionnaire-9) form to analyze any depressive symptoms that have resulted from the atopic dermatitis condition. This questionnaire is essential accompanied with prominent in displaying how atopic dermatitis can have a serious impact on mental health outcomes (behavior). In addition to this, participants will be given a DLQI (Dermatology Life Quality Index) to evaluate the influence of the condition on the participant's quality of life and daily functioning.

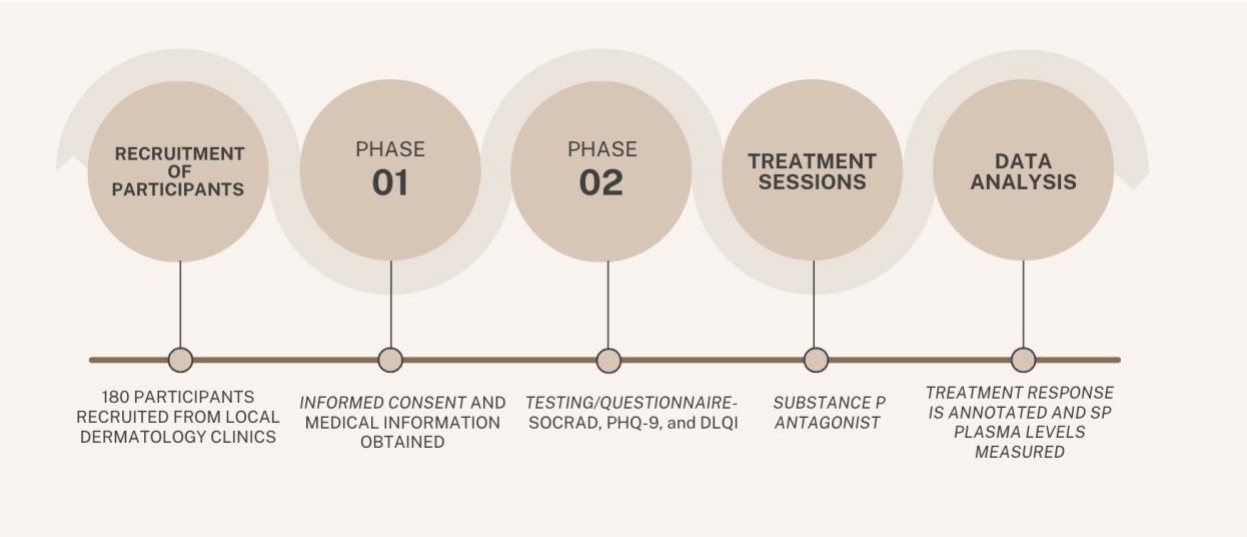
The treatment sessions involve participants taking one oral tablet of the Substance *P* antagonist daily, at a dosage of 80 mg. Children in the age ranges of 6-14 will have a lower dose of 45 mg to account for lower body mass composition. Participants will be asked to record any signs of itching, skin irritation, or signs of discomfort upon taking the tablet for the duration of the 4 weeks. Participants will be informed that if symptoms increase drastically, then medical assistance will be needed as well as provided immediately.

Phase III: Data Analysis

Following data collection, all dependent variables will be analyzed using statistical software (like SPSS). A repeated-measures ANOVA will be conducted to assess the interaction between time and treatment group for each dependent variable: itch severity, SCORAD index and IL-31 serum levels. This analysis will allow us to determine whether changes over time differ significantly between the treatment and control groups. If a significant interaction is found, post hoc paired-sample t-test will be conducted within each group to compare baseline and post-treatment scores. Effect to estimate the magnitude of treatments effects. The Substance *P* plasma levels will be measured through utilizing ELISA (enzyme-linked immunosorbent assay); in which blood samples will be collected to detect the peptides found within the plasma.

Participants will be debriefed regarding the results of the experiment accompanied with the statistical data.

Figure One:



This figure conveys the timeline of the intended experiment- in which it involves the stages of Recruitment, Phase 01, Phase 02, Treatment Sessions, and Data Analysis.

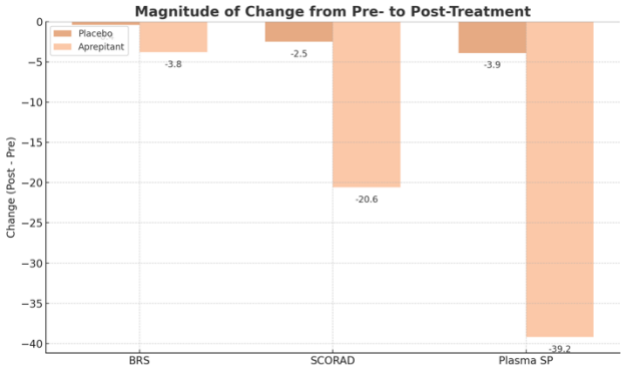
Figure Two:

Variable	Group	Pre-Treatment (Mean ± SD)	Post-Treatment (Mean ± SD)	Change
Behavioral Rating Score (BRS)	Placebo	7.8 ± 1.0	7.4 ± 1.2	-0.4
	Aprepitant	7.7 ± 1.1	3.9 ± 1.3	**-3.8**
SCORAD Index	Placebo	55.2 ± 6.1	52.7 ± 6.5	-2.5
	Aprepitant	54.8 ± 6.0	34.2 ± 5.8	**-20.6**
Plasma SP (pg/mL)	Placebo	89.5 ± 12.7	85.6 ± 13.0	-3.9
	Aprepitant	88.3 ± 11.9	49.1 ± 10.5	-39.2

This figure depicts mean change in itch severity scores from baseline to post-treatment in "Placebo" and "Aprepitant" groups. Error bars represent ±1 standard deviation.

The higher the negative numerical value is, the increase in reduced itch levels experienced by participants. This is evidently seen throughout the substantially negative values affiliated with the "Aprepitant" inspired treatment groups (Substance P antagonist) compared to the "Placebo" groups.

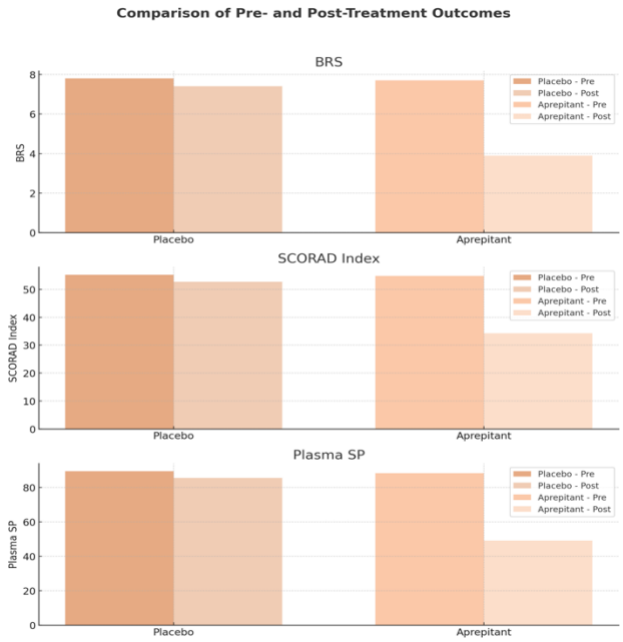
Figure Three:



The figure above displays the values of the magnitude of change (reduced itch levels) present within both groups before and after the treatment.

The Aprepitant-like treatment had a much greater effect as compared to the placebo treatment. This can be clearly seen by the increase in negative numbers throughout each examination (SCORAD, BRS, and Plasma SP levels).

Figure Four:



This figure demonstrates the side-to-side display of the outcomes for both groups prior and post treatment.

Alternative Results

In the instance that our findings do not follow our predictions, it is possible that results would not show a significant difference in subjective itch ratings and levels of inflammatory cytokines between the experimental group, those that received oral Aprepitant and control group, those that received a placebo. Moreover, there are other extraneous variables to consider when looking at subjectivity, severity of conditions and plasma levels. If the behavioral rating scale showed no improvement post-treatment, then this would induce that other stressors or life altering factors could have occurred. Another alternative result is the severity of itching and inflammation either increased or showed no significant difference this could be from life stressors as well as dealing with the condition itself being a battle to overcome. Lastly, Substance *P* plasma levels with no significant difference, would show that there may be other physiological or biological health concerns. The alternative result of our variables can allude to the

understanding of the multiple pathways that may be involved in atopic dermatitis, drawing a force on mediating g protein coupled receptors (GCPR) such as NK-1 and a bridge to explore brain-to-skin signaling.

Evaluation of Weakness/Future Directions

Although our experimental design and process includes individuals from a variety of backgrounds such as age, sex, gender, and ethnicity, we aimed to highlight mild to severe eczema in comparison to presentation of eczema as to see efficacy of treatment. However, previous research includes an addition of medication along with SP, to further inhibit itch and pain signaling such as GABA-a agonist and calcitonin gene-related peptide (CGRP) drugs (Yeo et al., 2022). A follow-up study can further enhance results of neuroimmune response of skin inflammation by targeting more than one treatment approach and solidifying a modality of medication with oral pills. Furthermore, our expected results of reduced itching, extent and severity of eczema and SP levels will engender a new focus of Substance *P* NK-1 antagonists.

Limitations:

- A short duration of treatment may not capture long-term effects.
- NK-1 antagonists may have off-target effects that influence outcomes

Future studies should examine:

- Longitudinal outcomes over 6-12 months
- Combination therapies with biologics

Understanding how neuropeptides like Substance P contribute to inflammatory skin diseases could open up a novel class of treatments. These therapies may be less immunosuppressive and more targeted, improving safety and accessibility for chronic disease management.

Conclusion

Current eczema treatments are focused mainly on resolving inflammatory problems without directly addressing the neural mechanisms that are related behind only itching. Since Substance *P* plays a key role in itch transmission in our nervous system, blocking it could provide a new and effective treatment strategy that does not only rely on steroids or immunosuppressants. Also, we believe an oral medication would be easier to take than creams or injections, making it more accessible for patients who struggle with traditional treatments available, which could be a new class of eczema treatments. By testing an oral Substance *P* antagonist, our goal is to determine whether this approach can effectively reduce itch severity and inflammation associated with atopic dermatitis, providing further synthesis of funding this research. Overall, understanding the relationship of how the nervous system interacts with the immune system in chronic skin conditions creates a powerful alternative for people that currently struggle with this condition every day of their lives.

Contributions

This work was proposed by Elysa Barrera in topic selection and following authors Yasmin Gebara and Nora Mourad. Yasmin Gebara contributed to this project by providing essential background research and methodology on atopic dermatitis and oral Substance *P.* Yasmin also included information of variables for the methods section and key points for future directions and conclusion. Nora Mourad contributed to this project by designing every step of our study methods according to previous research. Nora used in-depth methodological approaches using data figures to provide an excellent procedure for our proposed study. Elysa Barrera contributed to this through more extensive research to further support the alternative results, evaluation of

weakness/future directions and conclusion. Elysa also worked on evaluating the introduction and method sections.

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