THE ROLE OF CONFOCAL MICROSCOPY IN ESTIMATING DUPILUMAB TREATMENT RESPONSE FOR MODERATE/SEVERE ATOPIC DERMATITIS

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Research project summary

Atopic dermatitis (AD) is recognized as the most prevalent chronic inflammatory skin disease across all age groups. The introduction of reflectance confocal microscopy (RCM) signifies a substantial leap forward in the non-invasive skin assessment at a cellular level. This advancement can diminish the need for skin biopsies to diagnose and monitor skin diseases. Given the variability in the efficacy of systemic treatments for AD among patients, RCM emerges as an attractive tool for real-time monitoring of treatment response. This capability enables the treating physician to customize treatment approaches accordingly. There exists a lack of data concerning the subsurface characteristics of the skin explored with RCM before, during, and after dupilumab treatment in patients with moderate to severe AD.
Hypothesis: The characteristics of AD skin at the cellular level evaluated by RCM correlate with treatment response with dupilumab
Overall objectives: To evaluate the association between skin characteristics assessed by basal RCM and changes in EASI and vIGA-AD scores at 24 weeks in individuals with mod/sev AD treated with dupilumab.
Methods: Prospective cohort study. Forty patients with mod/sev AD starting dupilumab will be enrolled. Basal and periodic clinimetry, PROs, and evaluation of the affected skin through RCM will be done.
Expected results: To describe RCM phenotypes of responders and not responders to dupilumab
Impact: Offering the medical community a non-invasive tool to improve phenotypic characterization for tailoring clinical decisions. We strongly believe this could mark the initial stride towards adopting personalized medicine, ultimately resulting in enhanced therapeutic selection, dosage precision, optimized intervals, increased patient adherence, and reducing need for skin biopsies, particularly in infants.

Research plan

Research Background & Rationale

While skin is the most accessible organ for precise evaluation through biopsy, there is a clear interest in replacing biopsies with non-invasive techniques that offer insights into cutaneous physiopathology (Yew, J. Dermatol. Sci., 2019).
In this context, the introduction of reflectance confocal microscopy (RCM) marked a significant milestone in the non-invasive assessment of skin cancer, greatly enhancing the sensitivity and specificity of diagnosis, perioperative assessment, and follow-up for borderline lesions (Shahriari, J. Am. Acad. Dermatol., 2021). However, substantial progress remains to be made in the domain of inflammatory diseases, mainly atopic dermatitis (AD), where notable advancements have been achieved (Bratu, HealthcarePapers, 2023). Nonetheless, considerable opportunities for further developments persist. (Csuka, LSM, 2021) (Shahriari, J. Am. Acad. Dermatol., 2021).

RCM is a non-invasive imaging device with a cellular-level resolution akin to that of histopathology but in real-time. Consequently, It can monitor structural alterations in the stratum corneum, epidermis, and superficial dermis, as well as inflammatory cells, collagen, and vessels, making it possible to identify the degree and characteristics of inflammation and damage to the skin. Furthermore, as a non-invasive technique, RCM might be used for follow-up and clinical evaluation of many inflammatory diseases (Csuka, LSM, 2021).

Atopic dermatitis ranks as the most common chronic skin inflammatory disease across all ages groups. It is well established that the pathophysiology is driven by type 2 inflammation, mediated by interleukin-4 and interleukin-13 cytokines. It is well known that type 2 cytokines reduce microbial diversity, promote St. aureus colonization, influence keratinization, tight junctions' integrity, lipids' composition, filaggrin expression, and natural moisturizing factors. IL-4 and IL-13 play a critical role in the disruption of skin barrier function, affecting multiple skin barrier components and simultaneously being induced by barrier disruption (Beck, J Invest Dermatol, 2022; Hönzke, J. Invest. Dermatol., 2016).

Treatment guidelines developed by different Academies (Davis, J. Am. Acad. Dermatol., 2023; Larenas-Linnemann, Gac Med Mex, 2023) (Wollenberg, J. Eur. Acad. Dermatol. Venereol., 2023) 8-11) around the world recommend using systemic immunomodulatory agents for subjects in whom optimized topical regimens do not adequately control the signs and symptoms of the disease. These guidelines acknowledge that insufficient data exist to recommend optimal dosing, duration of therapy, and precise monitoring protocols for any systemic immunomodulating medication, including methotrexate and phototherapy, the most used drugs in our country for AD. In addition to the need for well-controlled efficacy data supporting their use in moderate to severe AD, the duration of use of many traditional systemic immunomodulatory agents is limited due to cumulative toxicity. Dupilumab has significantly improved symptoms, signs, and quality of life in patients with moderate to severe AD, incremental over time and with a favorable long-term safety profile (Simpson, N. Engl. J. Med., 2016) (Thomson, Br. J. Dermatol., 2018) (de Bruin-Weller, Br. J. Dermatol., 2018) (Beck, Am. J. Clin. Dermatol., 2022). Dupilumab has shown improvement in IGA 0-1 of 64.4% and EASI-75 in 90.9% of adult patients at 24 weeks, IGA 0 -1 of 42.7% and EASI-75 of 81.2% in pediatric patients at 52 weeks (Beck, Am. J. Clin. Dermatol., 2020) (Berdyshev, Allergy, 2022; Blauvelt, Am. J. Clin. Dermatol., 2022). In addition, recent data demonstrated that dupilumab improves skin barrier function with a microbiome diversity recomposition, normalizations of structural proteins and lipid composition of the skin barrier, epidermal water loss, etc. Dupilumab allows the restoration of skin lipid composition and barrier function in patients with moderate-to-severe AD. (Berdyshev, Allergy, 2022; Blauvelt, Am. J. Clin. Dermatol., 2022) (Callewaert, J. Invest. Dermatol., 2020) (Le Floc'h, Allergy, 2020).

Given that dupilumab is a disease-modifying drug for the skin barrier, accessing in vivo information regarding the subsurface before and during therapy through a non-invasive approach becomes essential. Delving into the epidermis, basal membrane, and upper dermis could offer a more comprehensive characterization and phenotyping of subgroups, thereby enabling a more accurate estimation of the treatment response in each subgroup.

To our knowledge, no data exist about the characteristics of the skin´s subsurface explored with a confocal microscope before, during, and after dupilumab treatment of moderate to severe AD patients.

Hypothesis

The characteristics of atopic dermatitis skin at the cellular level evaluated by reflectance

confocal microscopy correlate with treatment response with Dupilumab.

Objectives

Primary

To evaluate the association between skin characteristics assessed by basal RCM and changes in EASI and vIGA-AD scores at 24 weeks in individuals with moderate to severe atopic dermatitis treated with dupilumab.

Secondaries

1- To evaluate the association between skin characteristics assessed by basal RCM and the absolute response to treatment with predefined thresholds of EASI<10 and IGA (0,1) and EASI 75% at 24 weeks in individuals with moderate to severe atopic dermatitis treated with dupilumab.
2- To evaluate the association between skin characteristics assessed by basal RCM and treatment response assessed by clinimetry (vIGA-AD, EASI, BSA, PGIS, PGIC, SCORAD) and patient-reported outcomes (PP-NRS, SP-NRS, sleep disturbance-NRS, POEM, ADCT, and DLQI) at 24 weeks in individuals with moderate to severe atopic dermatitis treated with dupilumab.
3- To evaluate the association between other potential predictors and treatment response at 24 weeks in individuals with moderate to severe atopic dermatitis.
4- To estimate potential adverse events, adherence, and treatment switching rates in individuals with moderate to severe atopic dermatitis.
5- To describe the changes of the RCM over time in the entire cohort and subgroups of patients according to the type of response.
6- To compare skin changes in RCM over time in patients in treatment with dupilumab with healthy controls.

Detailed Research Plan

Methods

Design: Prospective cohort study

Setting, study population, and period

The Hospital Italiano is a non-profit civil association committed to delivering comprehensive healthcare services. Since its establishment in 1853, it has provided medical care, offered undergraduate and graduate students education, and actively engaged in fundamental, clinical, and population-based research. Annually, the hospital attends to 2.8 million consultations, oversees 46,000 patient discharges, and performs 52,000 surgical procedures. The Hospital has achieved accreditation from the Joint Commission International, certification from the College of American Pathologists, and holds a Level 7 status from the Health Information and Management System Society (HIMSS).
The Department of Dermatology encompasses over 110 faculties members, trainees, and

staff delivering outstanding patient care over 17 sites in Buenos Aires City, including inpatient and outpatient. Our department is one of the largest in Argentina and receives about 155,000 consultations in adult and pediatric dermatology annually. In addition, we have one of the most active teaching programs of any dermatology residency program in the nation. Within our department, we house various divisions and units. Notably, our Division of Immune Skin Disorders is dedicated to addressing a broad spectrum of autoimmune skin conditions, encompassing disorders such as psoriasis, bullous diseases, atopic dermatitis, lupus, suppurative hidradenitis, alopecia areata, among others. Our team comprises 12 exceptionally skilled and specialized dermatologists committed to delivering expert and innovative care in this field. Furthermore, we have actively engaged in the Atopic Dermatitis Quality of Care Initiative alongside 31 other institutions worldwide.
Through the Society of Dermatology of Argentina, the Society of Pediatric Dermatology and Project ECHO® (Extension for Community Healthcare Outcomes) AD group, dermatologists and allergists with a particular interest in treating patients with moderate-to-severe atopic dermatitis (AD) in the Buenos Aires Metropolitan Area will be invited to refer their candidate patients to the study before starting systemic medication.
The attending physicians, responsible for prescribing and monitoring patients' treatments, play a crucial role in this process. Specifically, the Buenos Aires Metropolitan Area boasts a tripartite healthcare system comprising the public sector, private healthcare providers, and social security institutions, with approximately 1800 dermatologists and allergists serving the region. To ensure a diverse participant pool, we aim to extend invitations to dermatologists and allergists across all healthcare institutions, irrespective of their insurance plans, prepayment systems, or socio-cultural backgrounds.
Approximately 14 million people live in the Buenos Aires Metropolitan Area. In recent publications, research showed the global prevalence and comorbidities in adults and those under 18 years of age in AD. The data showed that in adults, the prevalence is 3%, of which 0.3% were severe cases (Angles, An Bras Dermatol, 2022). The most common atopic comorbidity was rhinitis, while the most common non-atopic comorbidity was obesity (Angles, An Bras Dermatol, 2022). In children under 18, the global prevalence was 5%, with 0.52% suffering from moderate-to-severe disease (Antonietti, Arch Argent Pediatr, 2023). So, we estimate no severe difficulties, including the necessary number of subjects in 6-9 months.

Selection Criteria

Inclusion Criteria

- ≥ 6 months of age at the moment of inclusion in the study.
- Ability to give informed consent or assent and consent from parent/guardian in the case of pediatric patients.
- Subjects must meet Hanifin and Rajka's criteria of AD (Hanifin, Acta Derm Venereol, 1980).
- Moderate/severe AD at baseline taking 1 of the following 4:
EASI >16
Body surface area >10%
SCORAD > 25
vIGA-AD 3 o 4.
- Starting dupilimab for AD prescribed by their attending physician.
- In those with previous systemic treatment, a predefined wash-out time must be guaranteed:

for jaki: 4 weeks,
for oral steroids: 4 weeks,
for methotrexate: 4 weeks,
for phototherapy: 4 weeks

Exclusion criteria

- Patients who cannot comply with the study procedures
- Negative to consent.

Note: Ten healthy controls, five males and five females, will be included. To include healthy control patients, questionnaires to evaluate pruritus, xerosis, and inflammatory diseases and physical examination will be performed.

Procedures

Patients will be invited to participate by their attending physicians, and those interested will be referred to Hospital Italiano to explain the protocol and inform consent procedures. The study will include the visits detailed below and will last a maximum of 48 weeks. The protocol visits will be carried out at Hospital Italiano. Notably, the referral physician decides the treatment for each patient. As the coordinator center, the Hospital Italiano will collect information about clinimetry, PROs, and imaging. An external evaluator, Dr Giovanni Pellacani, a world reference in RCM, will define controversial findings.

Baseline

- Patient demographics and signature of the informed form.
- Previous medical history.
- Recording clinimetry (vIGA-AD, EASI BSA, PGIS, PGIC, SCORAD) and PROs (PP-NRS, SP-NRS, sleep disturbance-NRS, POEM, ADCT and DLQI)
- Recording of drug indicated and starting date—mode/route of administration, formulation and frequency of administration scheduled.
- Atopic dermatitis lesions localized on the trunk, extremities and face will be selected for RCM evaluation. The examination will not include extreme hyperkeratotic squamous or eroded acral lesions. For in vivo imaging, the Vivascope 1500 and 3000 (Vivascope, Rochester, NY, USA) will be used. The images obtained will be recorded in the database. RCM acquisition will be made with Vivascope 1500 by four mosaics (usually 5 mm × 5 mm) taken respectively at the level of the stratum corneum, the spinosum, the dermo-epidermal junction (DEJ), and the upper dermis. The RCM imaging protocol will include single images and stacks (from the corneal layer up to 250 μm) in affected areas. In lesions located in the face where it is impossible to attach Vivascope 1500, the examination will be done with Vivascope 3000.

Follow-up visits

The final visit will be at week 24 from baseline.

Variables

- Outcome variables: EASI, vIGA-AD, BSA, SCORAD, PP-NRS, SP-NRS, SD-NRS, POEM, ADCT, DLQI, PGIS, PGIC.
- Main predictive variables:
- Imaging variables: parakeratosis, disarrayed epidermis, hyperkeratosis, spongiosis, exocytosis, vesicles, acanthosis, non-edged dermal papillae, dermal-epidermal junction, dilated vessels, dermal infiltration, melanophages (see appendix for details). - Prior therapies and rescue treatments (see appendix for details).
- Descriptive variables: demographics, medical/surgery history, previous medications, atopic comorbidities, clinical phenotype, family history of AD, IgE level (see appendix for details).

Sampling and sample size

This exploratory study does not have a formal sample size estimation. We expect to include 40 consecutive patients on dupilumab therapy. Given that most of the potential participants would have a classical phenotype, we will do our best to include at least ten patients with the main phenotypes:
1- Classical: Lichenified/exudative flexural dermatitis, almost always associated with head-and-neck eczema and hand eczema
2- Generalized eczema with a lichenoid pattern: lichenification, excoriations, crusts, and xerosis
3- Nummular eczema with round, inflamed sores.

Statistical Analyses

Categorical variables will be presented as absolute numbers and percentages. Numerical variables will be presented as median and 25th-75th percentiles (IQR). We will use simple linear regression models using the delta of the scores between week 24 and baseline as the outcome variable to explore the association of the confocal microscope characteristics and treatment response. In addition, simple logistic regression models will be applied to assess the association between baseline characteristics and treatment responses classified as binary variables. Accordingly, we will report the beta coefficients or the odds ratio (OR) with their respective 95% coefficient intervals (CIs). The STATA v14.1 version will be used for analysis.

Ethical considerations

The study will follow the protocol, International Council for Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles in the Declaration of Helsinki. The protocol will be reviewed and approved by the local institutional review board (IRB) of Hospital Italiano. The informed consent form will be provided to the study participant on paper and must be signed by the participant or their legally authorized representative and investigator. The participant or their legally authorized representative must provide a copy of the ICF. The investigator must explain the nature of the study and answer all questions regarding the study. Participants must be informed that their participation is voluntary and that they can withdraw from the study when they desire. If

a participant decides to drop out of the study, it will not impact the management of their disease. The researchers will use all the information collected and images with the strictest confidentiality, considering the details of Law 25,326 on data protection. For this purpose, each patient will be registered with a consecutive number in a database to which only the leading researcher will have access.

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