CURRENT UNDERSTANDING OF ATOPIC DERMATITIS AND OPTIMAL CONTROL OF THIS DISEASE IN ADULT PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

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Summary

Atopic dermatitis is a chronic inflammatory disease that affects both children and adults, with complex and multiple consequences on the individual and on society. Its main mechanism of production is the type 2 inflammation, which involves T helper 2 cells and innate lymphoid cells, and is exerted through several cytokines with various effects, the most important being IL-4 and IL-13. The knowledge of these events, acquired in recent years, has led to the emergence of revolutionary therapies, which today manage the proper control of this disease, including its moderate and severe forms. Dupixent (Dupilumab) is the first such therapy – a human IgG4 monoclonal antibody that inhibits the signalling performed by the 2 cytokines mentioned above. The effects of this inhibition are multiple, including the fast, sustained and significant improvement of the signs, symptoms and quality of life of these patients, whether adults or teenagers with a minimum age of 12 years, under a favourable safety profile and without the shortcomings of a cortisone or immunosuppressive medication.

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What have we known about atopic dermatitis so far?

First of all, we knew that atopic dermatitis is a chronic, pruritic, recurrent inflammatory disease.

We also knew that it is a disease that affects both children and adults, with age-specific clinical features, and that it is characterized by pronounced dry skin, erythema, infiltration/papulation, crust/discharge and lichenification and, last but not least, intense, prolonged itching.

All the signs and symptoms of atopic dermatitis often have an important impact on several aspects of a patient's life: psychological, social and family aspects. Thus, we can say that atopic dermatitis substantially influences the life, education or work capacity of a patient who has this pathology, thus *involving* consequences both at the individual and at the societal level.

We also knew about atopic dermatitis that it is often difficult to control it (approximately 85% of patients report itching daily) and requires long-term, continuous treatment goals, translated into: prevention of exacerbations, management of comorbidities and secondary complications, minimization of side effects induced by conventional immunosuppressive treatments.

But what did we *NOT* know until now about atopic dermatitis or what was less known?

Perhaps less well known was the fact **that type 2 inflammation is the foundation of atopic dermatitis**, achieving a mechanism with a perfect connection between the skin's barrier function, the activation of immunity and the itching in this condition.

Therefore, today we know that skin barrier defects lead to the production of epithelial "alarms", which thus initiate the activation of the type 2 pathway. T-helper 2 cells and innate lymphoid cells (ILC2) migrate to the skin, where they produce type 2 inflammatory cytokines: IL-4, IL-13 and IL-5, associated with pruritus and

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disruption of skin barrier function; IL-31, dependent on autocrine IL-4 signalling on Th2 cells, also associated with pruritus. However, **the key and central drivers of type 2 inflammation in atopic dermatitis are still represented by the IL-4 and IL-13 cytokines.** IL-4 and IL-13 are mainly responsible for: reduced epidermal function, reduced antimicrobial proteins, reduced keratinocyte differentiation, reduced epidermal lipids, inadequate switching of IgE molecule classes, increased sensitivity to allergens, increased inflammatory cell recruitment and increased signalling of type 2 cytokines and chemokines.

The first molecule, the first biological treatment to target the mechanism of type 2 inflammation is **Dupixent (Dupilumab) – a human IgG4 monoclonal antibody**, which inhibits the signalling of the proteins interleukin-4 (IL-4) and interleukin-13 (IL-13), key factors of type 2 inflammation and involved in type 2 inflammatory diseases in humans (systemic allergic response), such as atopic dermatitis, asthma or chronic rhinosinusitis accompanied by nasal polyposis.

In 2016, the US Food and Drug Administration (FDA) designated **Dupixent (Dupilumab)** as "Breakthrough Therapy" for the treatment of patients with moderate to severe atopic dermatitis.

In Europe as well, **Dupixent (Dupilumab)** has 3 registered indications so far: **moderate to severe atopic dermatitis** (> *12 years*), **severe asthma** (> 12 years) and **chronic rhinosinusitis with nasal polyposis** (CRSwNP) (*adults*).

In addition to the currently approved indications, Dupilumab benefits from an extensive clinical development program, a program that studies and evaluates 8 other indications and which includes pathological fields in the areas of paediatrics, ENT, gastroenterology, pneumology and allergology.

Returning to atopic dermatitis, **Dupixent (Dupilumab)** is currently indicated for the long-term treatment of moderate to severe atopic dermatitis in adults and adolescents aged 12 years and older who are candidates for systemic therapy.

The efficacy and safety of **Dupixent (Dupilumab)** have been evaluated in a significant number of patients, so at this time, it is the molecule with the largest clinical development program in atopic dermatitis (adults and adolescents).

Inhibition of IL-4 and IL-13 signalling by **Dupixent (Dupilumab)** results in:

- Significant and sustained improvements in signs of atopic dermatitis, as measured by EASI-75 response rates
- Rapid, significant and sustained improvement in the symptoms of atopic dermatitis, as measured by Peak Pruritus NRS scores
- Multidimensional improvement of atopic dermatitis (signs, symptoms and QOL):
  - Most patients have achieved clinically significant improvements in at least one area
  - Improvements have been observed even in patients who did not get clear or almost clear skin (IGA score of 0 or 1)
- The clinical benefits of **Dupixent (Dupilumab)** were consistent across clinical trials in both adult and adolescent patients
- The safety profile of **Dupixent (Dupilumab),** evaluated in clinical trials, confirms and supports the fact that this is a molecule which is generally well tolerated and provides a favourable safety profile:
  - Injection site reactions and ocular pain were the most common side effects
  - Skin infections and serious or severe infections were less common in patients treated with **Dupixent (Dupilumab)**, as opposed to those receiving placebo.

Thanks to its mechanism of action, by blocking the IL-4/IL-13 pathway and reducing the mediators of type 2 inflammation, and unlike the treatments accepted and administered so far, **Dupixent (Dupilumab)** is not a steroid or immunosuppressive drug.

Last but not least, especially to meet the recommendations of the therapeutic guidelines - to set long-term, continuous treatment goals, it is worth mentioning here that in the real world, **Dupixent (Dupilumab)** is associated with high treatment persistence rates. Currently, world-wide and at the level of all approved indications, over 150,000 patients are treated with **Dupixent**

(Dupilumab) and almost 90% of patients who have started such therapy, are still in treatment, 2 years after its initiation.

Consequently, we can say today that, with the new discoveries of science, which allow us to understand better, more deeply this complex pathology that is atopic dermatitis, thanks to innovation and advances in medicine, we know new treatment opportunities and we have the possibility to offer our patients a normal, decent life, just the way they want it.

Conflict of interest
NONE DECLARED

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