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Is Dupilumab a chance for patients with moderate to severe atopic dermatitis? Literature review

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Abstract:

Introduction: Atopic dermatitis is an inflammatory disease which can significantly affect quality of life of patients. Especially severe forms of this disease are challenging to treat and for a long time forms of treatment have been limited. Because of that- it is crucial to find new ways of treatment which can be registered and improve moderate and severe dermatitis.

Aim of study: Fundament purpose of this literature review is focusing on effectiveness, safety, side effects or different potential medical applications of Dupilumab. The main question, which is formulated in the title- is Dupilumab a chance for patients with moderate to severe atopic dermatitis?

State of knowledge: Nowadays Dupilumab is well known drug and a lot of trials and analysis focus on efficacy, safety in treatment of moderate and severe dermatitis.

The development of Dupilumab and different potential, clinical applications is also a chance for other groups of patients- for example patients with asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis.

Conclusion: Dupilumab is definitely a relevant and essential element of treatment therapy for patients with moderate to severe atopic dermatitis. There were many analysis and researches which confirmed effectiveness, safety level and described Dupilumab impact on many different parameters and scales focused on symptoms and life quality of patients during treatment with Dupilumab.
Keywords: dupilumab, atopic dermatitis, skin, dermatology

Atopic dermatitis- definition, pathogenesis, symptoms, treatment

Atopic dermatitis is a chronic skin disease which direct reason is a disfunction of skin barrier. Skin barrier disfunction connected with immune dysregulation, environmental factors, infectious factors lead to development of atopic dermatitis. Some researches postulate also such factors as climate, pollution, gut microbiote, genetic conducive factors. Looking for potential factors, which can release a development of atopic dermatitis is crucial branch of researches. (1,2)

From year to year we have a bigger knowledge about pathogenesis of atopic dermatitis. There are many various researches about different potential factors and pathways- generally the main reason of development of atopic dermatitis are disruptions of epidermal barriers. It allows antigens to penetrate to deeper layers of the skin. It also activates epidermal inflammatory reaction and leads to releasing such inflammatory cytokines and catalyzers as IL-4, IL-13, IL-31. (3)

Atopic dermatitis symptoms may include- dry, cracked skin, itchiness. Hanifin- Rajka proposed diagnostic criteria of atopic dermatitis in 1980 and this diagnostic tool is still widely used- major criteria includes pruritus, typical morphology and distribution- flexural lichenification or linearity in adults, facial and extensor involvement in infants and children, chronic or chronically relapsing dermatitis, personal family history of atopy (asthma, allergic rhinitis, atopic dermatitis). There are also minor criteria which includes many elements- for example it is xerosis, raised IgE serum, food intolerance, Dennie- Morgan infraorbital fold, intolerance to wool and lipid solvents, white dermographism, nipple eczema, tendency toward non-specific hand or food dermatitis. (4,5,12,13)

Treatment includes changes in diet, lifestyle, phototherapic treatment, moisturisers, topical medications such as corticosteroids, topical calcineurin inhibitors- for example tacrolimus, pimecrolimus, systemic medications- ciclosporin, metotrexate, mycophenolate mofetil, azathioprine, interferon gamma- 1b. In 2017 FDA approved a new drug- Dupilumab to treat moderate to severe atopic dermatitis. In March 2023, the EMA- European Medicines Agency approved Dupilumab for the treatment of severe atopic dermatitis in children aged six months to five years. In the next part of this publication will be described different aspects of effectiveness, safety and different medical applications of Dupilumab.

Dupilumab- mechanism of action

Dupilumab is a humanized IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain, common to both IL-4R complexes- type 1 and type 2. Different signaling pathways coupled to the IL-4R complexes determine widening spectrum of applications of Dupilumab in modulating pathways involved in allergic diseases. The effect of Dupilumab is inhibiting IL-4 and IL-13 cytokine- induced responses, including the release of proinflammatory cytokines, chemokines, immunoglobuline E. Dupilumab as a human monoclonal antibody blocks signals of these central drivers of type 2 inflammation in multiple diseases. (6,7)

Dupilumab- effectiveness in atopic dermatitis, safety, side effects

First reports about Dupilumab found in Pub Med base are from 2013. Apart from different aspects of Dupilumab in atopic dermatitis group of patients, first reports focus also on possible application of Dupilumab among asthmatic group of patients.(8,9,10) Amount of reports about Dupilumab in Pub Med base increases year by year (38 found in base in 2016 and 884 found in Pub Med base in 2023). It shows that our level of knowledge about Dupilumab parameters, effectiveness and possibilities is higher year by year and also Dupilumab achieved wide popularity among researchers from different regions of the world. (15,16)

In 2014 Lisa Beck and co-authors performed randomized, double- blind, placebo controlled trials. Dupilumab was evaluated as monotherapy in two 4-week trials and in one 12-week trial and in combination with topical glucocorticoids in another 4-week study. (11) The conclusion was that patients treated with dupilumab had marked rapid and efficient improvement in evaluated measures of atopic dermatitis activity. The result of the 12- week study of dupilumab monotherapy: 85% of patients in the dupilumab group compared with only 35% in placebo group had a 50% reduction in the EASI score.

EASI is the Eczema and Severity Index- validated tool for the measurement of severity of atopic dermatitis. EASI divides the body into four regions. The head and neck are assigned 10% of the body surface area, the upper limbs 20%, the trunk 30%, lower limbs 40%. 40% of patients in Dupilumab group in this randomized, double- blind, placebo controlled trial as compared to 7% in placebo group achieved the lowest possible scores, so 0 or 1 in EASI.

Also in 2014 Jennifer Hamilton and co- authors performed transcriptomic analyses of pretreatment and posttreatment skin biopsy specimens from patients with moderate- to- severe atopic dermatitis treated weekly with 150 or 300 mg of Dupilumab or placebo. (14) It was the first report suggested and showing rapid improvement of atopic dermatitis molecular signature with targeted anti-IL-4 receptor therapy. Expression of genes upregulated in atopic dermatitis lesions decreased in patients treated with Dupilumab by 26% and 65% with Dupilumab 150 mg or 300 mg.

Initially, the reports and analysis focused mainly on adult population. Currently we have an access to more and more publications about effectiveness and safety among pediatric population of patients. For example recently because in January 2024 was published a pre-specified subgroup analysis of data for patients aged 6 months to 5 years with severe AD at baseline from a randomized, double- blind, placebo- controlled, phase III trial of Dupilumab. Amy Paller and co-authors included 125 patients and observed significant improvements with Dupilumab including mean 48.9% reduction in pruritus (17).

What is especially important no dupilumab-related adverse effects were serious or led to treatment discontinuation. It shows us an acceptable level of safety among pediatric patients. In March 2023, the EMA- European Medicines Agency approved Dupilumab for the treatment of severe atopic dermatitis in children aged six months to five years.

Side effects of Dupilumab include injection site reactions. Dupilumab can also cause allergic reactions or keratitis. Injection site reactions as side effects after different biological injections were measured in systematic review and meta-analysis made by Patrick Kim and co-authors (18). There were 16 biological included in meta-analysis across 80 eligible studies. The highest point prevalence of patients reporting injection site reactions were Canakinumab (15.5%) and Dupilumab (11.4%). For comparison the lowest site reactions rate was observed after injections of Risankizumab (0.8%) and Brodalumab (1.3%).

Obviously there are many other researches which focus on safety level and side effects rate during and after Dupilumab treatment. Lieneke Ariens and co-authors included 138 patients treated with Dupilumab (19).

What is especially crucial- their cohort was consisted of patients with very difficult to treat form of atopic dermatitis. 61% of this group of patients failed treatment on 2 or more immunosuppressive drugs. Treatment with Dupilumab significantly improved disease severity among this difficult group of patients. The EASI- 50 and EASI- 75 were achieved by 86% and 62% patients after 16 weeks of treatment. The most reported side effects was conjunctivitis, occurring in 34% of patients. Sarah Faiz and co-authors reported conjunctivitis in 38.2% patients during Dupilumab treatment (20). Firas Constantin Kreeshan and co-authors defined the most common side effects- eye symptoms occurring in 43.4% of patients and 16.3% developing conjunctivitis (21). This report included 30 weeks, 164 patients and EASI-75 was observed in 75% of patients. Longer, because, one year time range was included in Hideaki Uchida and co-authors single-center retrospective study. 61 patients were included in this report (22). The EASI score significantly decreased by a mean of 47.1% at 1 month, 70.4% at 3 months and 76.5% at 12 months. Conjunctivitis was observed in 21.3% of patients.

Medical application of Dupilumab - other groups of patients- asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis

Atopic dermatitis is main disorder, which is mentioned in the title of this article and it is most widely described in this article, but there are also some others pathways of researches and possible medical application of Dupilumab. This part will be dedicated to other conditions and disorders which are analyzed in the Dupilumab context. Nowadays, Dupilumab is FDA-approved not only for atopic dermatitis, but also for different multiple indications, including treatment of asthma (23), chronic rhinosinusitis with nasal polyps (27), eosinophilic esophagitis and prurigo nodularis.

Clairelyne Dupin and co-authors describe effectiveness and safety of Dupilumab for the treatment of severe asthma in French adult cohort (25). An early access program for Dupilumab was opened in France in severe asthma patients experiencing unacceptable steroids side-effects. In this cohort Dupilumab significantly improved asthma control and reduced oral steroids use. After 12 months of treatment asthma control test improved from 14 to 22.

Dupilumab was also checked in the context of asthma among pediatric population. Leonard Bacharier and co-authors organized 52 week randomized, double-blind, placebo-controlled trial who had uncontrolled moderate- to severe asthma, they received a subcutaneous injection of Dupilumab- 100 mg dose for children <30 kg and 200 mg dose >30 kg) or matched

placebo every 2 week (24). The mean change in the ppFEV1- forced vital capacity, so the volume of air that can forcibly be blown out after full inspiration, was 10.5 percentage points with dupilumab and 5 percentage points with placebo. The conclusion is that children treated with dupilumab gained better lung function than placebo.

The effectiveness and safety of Dupilumab was also checked among patients with chronic rhinosinusitis with nasal polyps. Tobias Albrecht and co-authors enrolled 81 patients of whom 68 were still receiving Dupilumab after 1 year of follow-up (26). The polyp score decreased substantially during follow-up and parameters for disease- related quality of life and sense of smell increased significantly. Only 1 patient discontinued therapy due to severe side effects.

In May 2022, the U.S. Food and Drug Administration granted approval for Dupilumab for people ages 12 and older with eosinophilic esophagitis (EoE). EoE is characterized by the presence of eosinophils, a specific type of white blood cell, in the esophageal tissue. Evan Dellon and co-authors conducted a three part, phase 3 trial with randomization. Histologic remission occurred in 60% (25 of 42 patients) who received weekly Dupilumab and 5% (2 of 39 patients) who received placebo (28).

Prurigo nodularis is a skin disease characterized by pruritic nodules which usually appears on the arms or legs. FDA has approved Dupilumab injection for the treatment with prurigo nodularis in 2022. Gil Yosipovitch and co-authors described randomized, double-blind, placebo controlled phase 3 trials. The primary endpoint was pruritus improvement measured by proportion of patients with >4 points reduction in Worst Itch Numeric Rating Scale. A >4 points WI-NRS reduction at week 24 in the dupilumab and placebo was achieved by 60% and 18.4% patients (29,30).

Summary

Dupilumab is a very valuable, therapeutic option for people with atopic dermatitis. Recent years bring us a respectable amount of new reports about Dupilumab effectiveness, safety and applications among different groups of patients with atopic dermatitis. There are also more paths and branches of researches about Dupilumab and because of that Dupilamab effectiveness and safety is also checked in such diseases as asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis. Using Dupilumab is definitely a big chance for patients with moderate and severe acute dermatitis to improve their skin symptoms and general quality and standard of life.

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Author's contribution:

Conceptualization- Paweł Iwańczuk

Formal analysis- Paweł Iwańczuk

Investigation- Paweł Iwańczuk

Writing- rough preparation- Paweł Iwańczuk

Writing- review and editing- Paweł Iwańczuk

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