REAL-LIFE EXPERIENCE IN THE EFFECTIVENESS, IMPACT ON QUALITY OF LIFE AND SAFETY OF DUPILUMAB TREATMENT IN PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS IN THE CZECH REPUBLIC

Milena Tánczosová[1], Martina Kojanová[2], Monika Arenbergerová[1], Petr Arenberger[1], Tomáš Doležal[3], Daniela Štrosová[3], Jorga Fialová[2], Spyridon Gkalpakiotis[1]

[1]Department of Dermatovenereology, Charles University, Third Faculty of Medicine and University Hospital of Královské Vinohrady, Prague, Czech Republic

[2]Department of Dermatovenereology, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[3]Value Outcomes, Prague, Czech Republic

SUMMARY

Objectives: The aim of the study was to assess the effectiveness and safety of dupilumab therapy in patients with moderate-to-severe atopic dermatitis (AD) in a real-life Czech bicentric cohort.

Methods: We retrospectively analysed 50 patients with moderate-to-severe AD treated with dupilumab in two centres in the Czech Republic. Baseline characteristics, the Eczema Area and Severity Index (EASI) score and Dermatology Life Quality Index (DLQI) were collected at baseline and each 3 following months. The proportion of patients achieving EASI50, EASI75, EASI90 and EASI100 were analysed. Levels of immunoglobulin E (IgE) were collected before and after 6 and 12 months of therapy. Adverse events were recorded as well.

Results: Thirty-two men and 18 women with mean body mass index (BMI) of 25.7 were enrolled in our analysis. The mean age of the patients was 37.6 years and the mean time from diagnosis until the initiation of dupilumab therapy was 35.0 years. After 4 months, EASI75 was achieved by 75.7%, out of which 40.5% achieved EASI90 and 10.8% achieved complete clearance. Improvement continued with time, and the proportion of patients with EASI90 increased to 71.4% at the 6th month and at the 12th month of therapy the EASI90 was 65.2%. EASI100 was achieved by 14.3% and 13.0% at the 6th and 12th month, respectively. A marked reduction was observed in the DLQI and also in IgE levels. EASI responses were independent of BMI. No new safety issues were identified. Adverse events were experienced by 44% (22/50) of the patients and they were all mild in intensity. Conjunctivitis and herpes simplex virus infection were the most common adverse events.

Conclusion: Our results confirmed the effectiveness and safety of dupilumab in a real-life setting in adult patients with moderate-to-severe AD in the Czech Republic. Dupilumab was well-tolerated and resulted in a significant clinical improvement in combination with improvement of quality of life.

Key words: atopic dermatitis, dupilumab, biological treatment, real-life, conjunctivitis

Address for correspondence: M. Tánczosová, Department of Dermatovenereology, Third Faculty of Medicine, Charles University and University Hospital Královské Vinohrady, Ruská 2411, 100 00 Prague 10, Czech Republic

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INTRODUCTION

Atopic dermatitis (AD) is a multifactorial non-infectious chronic inflammatory skin disease, with a prevalence of 1 to 3% in adults and 15 to 20% in the world's paediatric population, posing a significant burden on patients' quality of life (1). The clinical picture of atopic dermatitis as well as the course of the disease itself is diverse but the basic characteristic triad of the disease is persistent pruritus, dermatitis and xerosis. In most cases, atopic dermatitis manifests itself in the first three years of life, when in 70% of cases complete spontaneous remission occurs before reaching adulthood, and in the remaining cases the disease persists into adulthood mostly in the form of remissions and relapses (2). Although skin barrier defects and altered immune responses are accepted as key components in disease development, the full pathophysiology remains unclear.

Two hypotheses are now known regarding the development of inflammation that leads to atopic dermatitis.

The first hypothesis is primarily immune dysfunction – increased expression of Th 2 lymphocytes and thus interleukins 4 (IL-4) and 13 (IL-13), which results in immunoglobulin E (IgE) sensitization, allergic inflammation and secondarily epithelial dysfunction.

The second hypothesis assumes impaired epithelial skin function as the primary disorder which leads to immunological

dysregulation and then to inflammation (3). Genetic and environmental factors are also involved in the expression of AD.

The treatment of moderate-to-severe atopic dermatitis is complicated and lengthy. It aims to reduce the symptoms and extent of the disease by reducing its severity, preventing or reducing exacerbations, minimizing the risks of the treatment itself and improving the patient's quality of life.

For moderate-to-severe AD, the efficacy of topical therapy is often limited and approximately 10–20% of adults with AD do not respond adequately and require phototherapy and/or systemic therapy. The only approved immunosuppressive drug for the treatment of AD is cyclosporine (4, 5).

Dupilumab is the first approved fully human monoclonal antibody for the treatment of moderate-to-severe atopic dermatitis. It blocks IL-4 receptor-α subunit, thereby inhibiting the signalling of both IL-4 and IL-13 (6). Clinical trials demonstrated efficacy and safety of dupilumab. However, studies on real-life experience are still limited (7, 8). Objective of our study was the retrospective assessment of dupilumab effectiveness and safety in a real-life Czech bicentric cohort of patients with moderate-to-severe AD as well as change on quality of life.

METHODS AND MATERIALS

We retrospectively collected data of 50 patients with moderate-to-severe AD treated with dupilumab from September 2018 to December 2020 from two dermatological centres for biological treatment in Prague, Czech Republic. Every patient who received at least one dose of dupilumab was included.

Baseline characteristics were demographic variables including body mass index (BMI), comorbidities, AD form, age of onset of AD, previous treatments, and date of initiation of dupilumab. Two validated scores, the Eczema Area and Severity Index (EASI) and Dermatology Life Quality Index (DLQI) at baseline, on week 16, 24, and then every 6 months were recorded. The total serum IgE level was also analysed when available.

Electronic medical records from both dermatological centres were reviewed to collect the data.

The epidemiological data (i.e., demographic and disease characteristics, medical history), disease severity (EASI, DLQI), BMI, comorbidities, previous treatments, and adverse events were summarized using descriptive statistics. Descriptive statistics were used to evaluate the dataset based on the number of patients and their percentage proportion in groups relative to categorical variables; the mean and standard deviation were used for continuous variables. The effectiveness of treatment was evaluated at baseline, and then at the 4th, 6th and 12th month of therapy in terms of mean percentage change from baseline and percentage of patients with an EASI reduction $>50\%$, $>75\%$ and $>90\%$ from baseline (EASI50, EASI75, EASI90). Based on the nature of the data, Wilcoxon matched-pairs signed-rank or paired t-test were used to evaluate differences between baseline and follow-up visits. Two-sample test of proportions was used to test the difference in proportions. The statistical testing was done on the 5% level of statistical significance.

RESULTS

Demographics and Clinical Characteristics

The study population included a total of 50 patients (32 men and 18 women) with a mean age of 37.6 years (SD 11.4, range 16–75). The average BMI of the patients was 25.7 (SD 4.8, range 18.9–40.9).

Mean age at the onset of atopic dermatitis was 2.2 years (SD 4.0, range 0.0–20.0), the mean age at the initiation of dupilumab treatment was 37.1 years (SD 11.3, range 16.0–74.0). Allergic comorbidities were mostly represented by allergic rhinitis (76%), food allergy (71.5%), asthma (57.1%), and ocular comorbidities (52.0%), out of which atopic conjunctivitis and keratitis were the most common. Other comorbidities were less frequent; arterial hypertension (18%), glaucoma (10%), dyslipidaemia (8%), and chronic kidney disease (6%). Majority of the patients (78%) were non-smokers, out of them 8% were ex-smokers.

Prior to starting dupilumab, all 50 patients (100%) had been treated with conventional systemic therapy. The majority of patients had been treated with cyclosporine (98%), followed by phototherapy (narrowband UVB) (64%), oral corticosteroids (42%), azathioprine (26%), methotrexate (18%), and mycophenolate mofetil (1%).

The mean EASI score at baseline was 32.0 (SD 9.4), the highest being 60.0. Quality of life was impaired before initiation of therapy with an average DLQI score of 20.1 (SD 4.8) (Table 1).

Dupilumab Treatment

Out of 50 patients, 37 patients completed 4 months of treatment, 35 completed 6 months, and 23 patients 12 months. All patients received at least one dose of dupilumab. One woman discontinued the treatment due to pregnancy.

There was a significant reduction in EASI and DLQI scores between baseline and follow-up visits after 4, 6 and 12 months of treatment. At baseline, the mean EASI score was 32.0 (SD 9.4) and was significantly reduced to 4.6 (SD 4.0, $p<0.001$) after 4 months and after 6 months the score dropped further to 2.8 (SD 2.5, $p<0.001$). At 12 months the EASI score was 2.7 (SD 1.8, $p<0.001$). EASI90 response was observed in 19 (51.4%), 25 (71.4%), and 15 (65.2%) patients after 4, 6 and 12 months, respectively. After 4 months the EASI100 response was achieved by 4 (10.8%) patients, after 6 months by 5 (14.3%), and after 12 months by 3 (13.0%) patients. Mean DLQI score was 20.1 (SD 4.8) at baseline and decreased to 4.8 (SD 3.9, $p<0.001$) after 4 months, to 3.4 (SD 2.9, $p<0.001$) after 6 months, and to 2.6 (SD 2.1, $p<0.001$) after 12 months of treatment (Figure 1, 2).

Total IgE serum levels were available in 14 out of 50 patients at baseline, in 8 out of 35 patients at the 6th month of therapy, and 7 out of 23 patients at the 12th month of therapy. At the baseline visit the mean of total IgE serum level was 15,513 IU/ml (range 1,940–42,100) and was markedly reduced to 6,879 IU/ml (range 1,350–21,600) at 6 months. At 12 months the mean serum level of IgE further dropped to 5,827 IU/ml (range 452–21,900). Due to the small number of observations, differences in IgE were not tested.

Furthermore, we analysed the association between BMI and the treatment response measured by EASI75 and EASI90. The results showed that BMI was not significantly associated with

***Table 1**. Demographic and clinical patients' characteristics (50)*

Characteristics	n (%)
Number of patients	50 (100.0)
Men	32 (64.0)
Age (years), mean (SD)	37.6 (11.4)
Age at the time of diagnosis (years), mean (SD)	2.2 (4.0)
Age at the time of initiation of dupilumab (years), mean (SD)	37.1 (11.3)
Family history of AD (yes)	26 (52.0)
Smokers (yes)	11 (22.0)
Allergic comorbidities (yes)	42 (84.0)
Rhinitis	32 (64.0)
Food allergy	30 (60.0)
Asthma	24 (48.0)
Ocular comorbidities (yes)	26 (52.0)
Atopic conjunctivitis	8 (16.0)
Keratitis	8 (16.0)
Keratoconus	7 (14.0)
Infectious keratitis	7 (14.0)
Atopic keratoconjunctivitis	6 (12.0)
Other comorbidities (yes)	32 (64.0)
Hypertension	9 (18.0)
Glaucoma	5 (10.0)
Previous systemic treatment (yes)	50 (100.0)
Cyclosporine	49 (98.0)
Phototherapy	32 (64.0)
Oral corticosteroids	21 (42.0)
Azathioprine	13 (26.0)
Methotrexate	9 (18.0)
Other treatment	5 (10.0)
Baseline BMI (kg/m^2), mean (SD)	25.7 (4.8)
Baseline EASI, mean (SD)	32.0 (9.4)
Baseline DLQI, mean (SD)	20.1 (4.8)
Baseline BSA, mean (SD)	55.7 (17.2)
Length of dupilumab treatment (months), mean (SD)	10.3 (6.8)
Duration from diagnosis to initiation of dupilumab (years), mean (SD)	35.0 (11.8)

AD – atopic dermatitis; BMI – body mass index; EASI – Eczema Area and Severity Index; DLQI – Dermatology Life Quality Index; BSA – Body Surface Area

either EASI75 or EASI90 (all $p>0.05$). At the 4th month of therapy 78.9% of patients with BMI below 25 reached EASI75 and 72.2% of patients who had BMI above 25 reached EASI75. EASI90 was achieved by 47.4% of patients with BMI below 25 and by 55.6% patients who had BMI above 25 at the 4th month of treatment. At the 6th month of therapy 68.4% of patients with BMI below 25 and 75.0% patients with BMI above 25 achieved EASI90. At the 12th month of therapy 63.6% patients with BMI below 25 and 66.7% of patients with BMI above 25 still had EASI90 (Fig. 3).

Dupilumab Safety Profile

Dupilumab was generally well tolerated. At least one adverse event was experienced by 44% (22/50) of the patients. They were all mild in intensity and were not considered to be directly related to dupilumab. No deaths occurred during the study. Conjunctivitis (4 cases) and herpes simplex virus infections (4 cases) were the most common side effects, followed by 3 very mild COVID-19 infections, 2 cases of non-infectious keratitis, folliculitis and transient eosinophilia, 1 mild urinary tract infection, 1 headache after dupilumab administration, 1 solar urticaria, 1 herpetic keratitis, 1 erysipelas, 1 acne vulgaris, 1 endometriosis, and 1 pulpitis. Seven patients with ophthalmic complications were referred to an ophthalmologist for proper treatment.

One woman temporarily discontinued the treatment due to pregnancy.

DISCUSSION

Dupilumab has been reimbursed in the Czech Republic since June 2019. Up to now limited "real-world" data has been published (7). The acquisition of this data is inevitable and crucial to the treatment of patients with atopic dermatitis, as the cohort of patients in the randomised trials are well chosen and not representative of the general AD population.

A real-world retrospective study was previously conducted in France, and it evaluated dupilumab treatment outcomes in 241 patients after 12 weeks of treatment. The authors measured baseline AD activity score and pruritus intensity at baseline and at 12 weeks and noted improvement in both measures in their patient population. They reported 84 cases of conjunctivitis and no severe adverse effects (8).

A retrospective multicentre study including 109 patients in Italy also showed significant reductions in AD severity from baseline to week 4 and a further significant decline in week 16, adverse events were experienced by 21 (19.2%) of the patients and they were all mild in intensity, conjunctivitis being the most common side effect (9).

These findings are in agreement with our study. Before dupilumab, all our patients received at least one previous systemic treatment, the most common was cyclosporine (98%). This is simply due to the fact that cyclosporine is the only on-label therapy for the treatment of moderate-to-severe atopic dermatitis, all other systemic drugs are off-label.

In our patient population, dupilumab showed good efficacy and was well tolerated. The effectiveness of dupilumab was expressed by a significant reduction of EASI (Fig. 1) and DLQI scores (Fig. 2), marked decrease was observed also in total IgE serum levels.

After 4 months, EASI90 response was seen in 51.4% of the patients, which further increased after 6 months (71.4%), and after 1 year it decreased to 65.2%. EASI90 response was higher in our study (63.8%) after 4 months compared to the results at 16 weeks of the SOLO-1 (35.7%), SOLO-2 (30.0%) and CHRONOS (39.6%) trials (11). This could be due to the fact that the population characteristics are well-chosen in the clinical trials. Furthermore, in SOLO-1 and SOLO-2 trials, patients could not use background topical corticosteroid (CS) therapy, in CHRONOS the topical steroid therapy was allowed, but patients

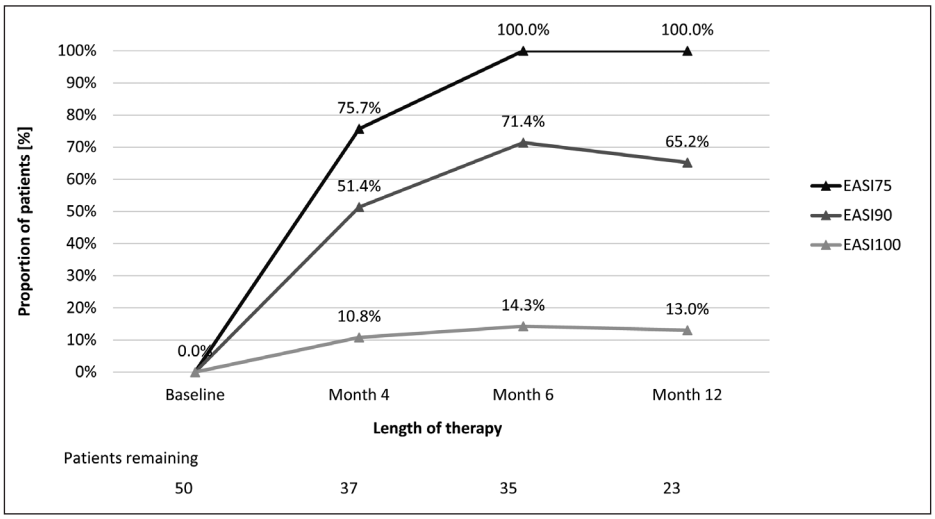

Fig. 1. *Percentage of patients achieving EASI75, EASI90 and EASI100 at month 4, 6 and 12 compared to baseline.*

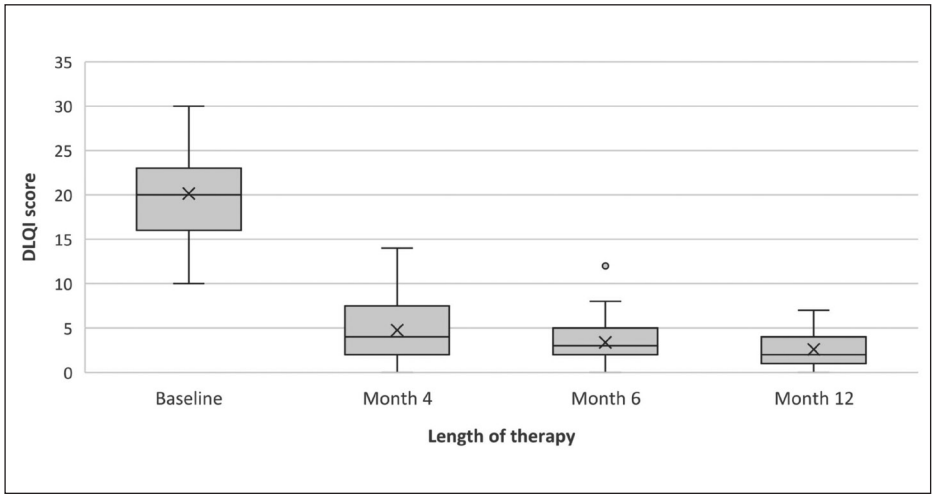

Fig. 2. *Development in improvement in DLQI score at baseline and month 4, 6 and 12.*

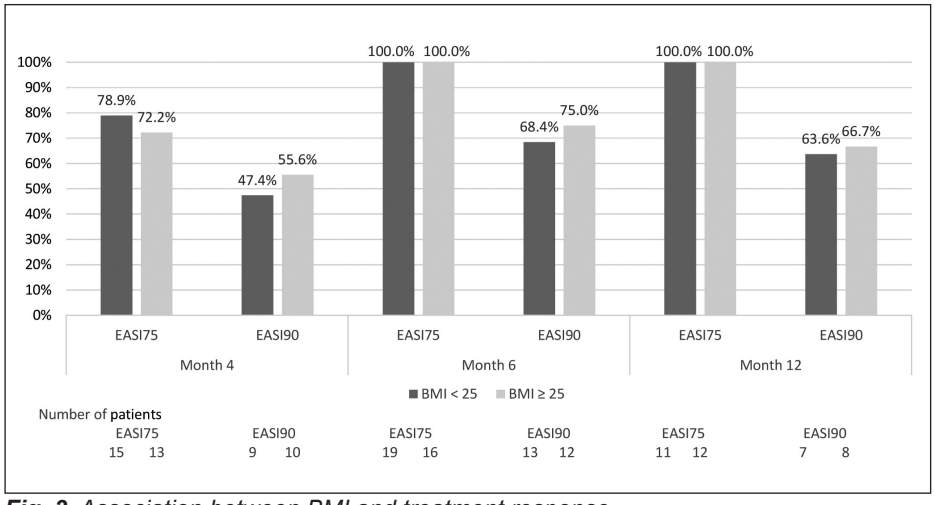

Fig. 3. *Association between BMI and treatment response.*

could only use medium-potency CS for a short term. In our study the patients were allowed a broad spectrum of background therapy including not only medium-potency CS, but also high-potency CS, calcineurin inhibitors, or were allowed short-term treatment of systemic corticosteroids in case of exacerbation. Concomitant treatment with topical anti-inflammatory agents is common practice in the real-life dermatological setting and our results are indeed in line with other real-life studies.

The percentage of patients with EASI75 (75.7%) at the 4th month was higher in our study compared to that observed in a real-life study by Faiz et al., where EASI75 at the 4th month was reached by 60.6% (8).

In our study EASI75 was achieved by 75.7% patients at 4 months, out of which 40.5% achieved EASI90 and 10.8% achieved complete clearance.

Dupilumab significantly improved patients' quality of life represented by DLQI score which showed reduction by 76.1% at the 4th month of therapy, followed by further reductions at the 6th and 12th months.

The average BMI at the baseline visit was 25.7 (SD 4.8). We compared the EASI75 and EASI90 scores with patients who had BMI above and below 25 and we found no significant difference, which means that dupilumab is effective not only in patients who have normal weight but also in overweight patients.

The dupilumab safety profile in our real-life patients was similar to that reported in clinical trials. No new safety signals were observed. Conjunctivitis and infections caused by herpes simplex virus (4/4) were the most common adverse events, observed in 8% of our patients, all mild in intensity, without the necessity to initiate systemic therapy. Conjunctivitis was reported in 8.6–22.1% of AD patients in 11 dupilumab trials (12) and ranges up to 40% in real-life studies (8, 9).

Furthermore, due to the current epidemiological situation, we reported three patients who were infected with mild SARS-CoV-2, therapy with dupilumab was not interrupted.

Improvement of EASI and DLQI was mainly observed within the first 6 months of treatment. No further improvement was seen between 6 and 12 months of therapy which could be due to the low number of patients.

Dupilumab therapy reduced total IgE serum concentrations in our real-life data. This is due to the fact that dupilumab blocks IL-4 and IL-13 which are known to increase IgE production (13).

A limitation of our study is that our data was collected from a routine patient management environment in a retrospective manner which could result in confounding and selection bias and the relatively small number of patients.

In conclusion, our data suggest that dupilumab is effective and safe in the treatment of moderate-to-severe atopic dermatitis. Further studies with a higher number of patients and a longer follow up are necessary to confirm our experience.

CONCLUSION

This retrospective analysis confirmed the effectiveness and safety of dupilumab in a real-life setting. Dupilumab was well-tolerated and resulted in a significant clinical improvement in combination with improvement of quality of life. However, further studies with larger number of patients are needed to assess this drug's long-term effectiveness and safety.

Conflict of Interests

Milena Tánczosová has served as investigator for Novartis, Leo Pharma, Pfizer, Galderma and Amgen. Martina Kojanová, Jorga Fialová, Tomáš Doležal and Spyridon Gkalpakiotis have served as consultants, speakers, or investigators for AbbVie, Amgen, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer, Sanofi, and UCB. Petr Arenberger has served as consultant, speaker, or investigator for Abbvie, Amgen, BMS, Eli Lilly, Janssen, Leo Pharma, L'Oréal, MSD, Novartis, Pfizer, Pierre Fabre, Sanofi, and UCB. Monika Arenbergerová received honoraria from Abbvie, MSD, BMS, Novartis, L'Oréal, and Pierre Fabre.

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Adherence to Ethical Standards

The study was conducted in accordance with the Helsinki Declaration of 1964 and all subsequent amendments, and all patients provided written informed consent. Patient-level data used for this analysis were deidentified, the Institutional Review Board approval was not required for this study.

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