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Implementation of dupilumab in routine care of atopic eczema. Results from the German national registry TREATgermany.

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Dear Editor,

The German atopic eczema (AE)-registry TREATgermany is a non-interventional multicenter patient cohort study for adult patients with currently moderate-to-severe disease activity or current/previous anti-inflammatory systemic treatment.[1,2]

Dupilumab has demonstrated to be an effective treatment for patients with moderate-to-severe AE in clinical trials.[3-5] Real world evidence is now needed to evaluate its effectiveness and safety in routine care.

Here, we describe first results of an interim analysis of the TREATgermany registry regarding the implementation of dupilumab as a new treatment option in routine care.

Between 06/2016 and 01/2019 612 patients (mean age 42.6 years, 38.2% female) were enrolled by 32 recruitment sites centers (16 hospital outpatient departments and 16 registered dermatological offices).[2] Since 12/2017, when dupilumab was launched in Germany, 200 registry patients received a new systemic therapy within routine care. 174 of these patients received dupilumab, which in 137 patients was not switched from another systemic agent, so that a systemic treatment-free baseline value was available. In 35/137 patients (25.5%) dupilumab was the first systemic therapy ever, while 102/137 patients were exposed to at least one systemic therapy prior to enrollment in the registry. 32.8% (45/137) had previous therapy with oral corticosteroids only and 35.8% (49/137) were exposed to ciclosporin prior to treatment with dupilumab.

Patients who received dupilumab during registry observation (n=137) had a high disease activity at baseline with mean Eczema Area Severity Index (EASI) and objective Scoring Atopic Dermatitis (oSCORAD) score of 22.9±13.6 and 48.0±15.7, respectively. 40.9% and 63.8% of the patients treated with dupilumab suffered from “(very) severe” disease based on the EASI (>= 23.0) and Investigator Global Assessment (IGA; severe: 4 or 5).

As TREATgermany is an ongoing registry, information from 3-month and 6-month follow-up visits was available from 105 and 53 patients, respectively, at the time of database lock (Table 1). EASI-50, EASI-75 and EASI-90 response rates were 77.1%, 57.1%, and 25.7% after 3 months. At month 6, EASI-50, EASI-75 and EASI-90 response rates were 85.2%, 51.9%, and 31.5%. oSCORAD response rates were slightly lower (oSCORAD 54.7% mean percent change after 3

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months) compared to EASI response rates (EASI 74.2% mean percent change after 3 months), most likely due to the different weighing of disease extent and severity items without scoring crusting/oozing by EASI. IGA 0 or 1 (clear/almost clear) was seen in 29.5% and 33.3% of the patients at month 3 and 6.

The mean Patient Oriented Eczema Measure (POEM) reduction was 54.5% at month 3, while the average itch intensity and sleeping problems over the past 3 days improved by 57.8 and 72.2%. The mean Dermatology Life Quality Index (DLQI) score showed a decrease from 12.4±6.7 at baseline to 4.4±5.2 and 4.2±4.5 after 3 and 6 months of treatment ($p<0.001$ for both comparisons). The proportion of well and completely controlled weeks (assessed by patients) improved from 27.5% and 5.0% at baseline to 70.8% and 47.5% after 3 months and 79.2% and 52.5% after 6 months. Further, the degree of skin dryness as assessed by the SCORAD and the POEM showed significant improvements.

Also the use of topical anti-inflammatory treatment decreased during dupilumab therapy. At initiation of treatment 92.4%, 34.3% and 41.9% were on topical corticosteroid (TCS), pimecrolimus, and tacrolimus treatment, respectively. After 3 months, these proportions were reduced to 46.7%, 10.5%, and 16.2%. In addition, in 48.8% of patients the application of TCS in a reactive application regime could be stopped and the proportion of proactively treated patients was doubled (26,7% after 3 months).

Only 12.4% of patients treated with dupilumab did not show a clinically meaningful response in any of the major outcome domains (EASI-75, ≥ 4 Numeric Rating Scale (NRS) points reduction in weekly average itch, ≥ 4 points reduction in DLQI score), which is comparable to the recently published results of non-responders in a Dutch registry (11%).[6] Response was not significantly associated with any clinical characteristic, but there was a trend for higher response rates in patients with higher disease activity at baseline.

Three months after the initiation of treatment with dupilumab, conjunctivitis was reported in 13.3% of patients (n=14/105). This rate increased to 22.6% (n=12/53) after 6 months of dupilumab exposure. The proportion of patients developing new onset or worsening of conjunctivitis was comparable to previous phase 3 clinical trials (9-28%)[3-5] and lower than in reported routine care patient cohorts (34-62%).[6-8]

In conclusion, observations from this real-world patient population indicate no major efficacy-effectiveness gap for dupilumab, but largely confirm trial data. As the registry continues, more comparative real-world evidence on immunomodulatory therapies will become available.

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Table 1: Effectiveness of dupilumab in patients with first exposure to dupilumab within registry observation period and at least 3 months patient individual follow-up after first dupilumab prescription (n=105), mean age 44.6 years, 32.4% female.

	Patient-individual baseline before dupilumab exposure (n = 105)	Patient-individual 3 month follow-up (n = 105)	Patient-individual 6 month follow-up (n = 53) **

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EASI - mean (SD) - EASI 50-Response - EASI 75-Response - EASI 90-Response	23.6 ± 14.3	6.1 ± 6.1 p < 0.001* 77.1 % 57.1 % 25.7 %	5.1 ± 4.9 85.2 % 51.9 % 31.5 %
Objective SCORAD - mean (SD) - oSCORAD 50-Response - oSCORAD 75-Response - oSCORAD 90-Response	49.2 ± 15.1	22.3 ± 11.4 p < 0.001* 57.4 % 20.0 % 4.8 %	22.0 ± 11.4 48.1 % 16.7 % 7.4 %
Investigator Global Assessment (IGA)	3.8 ± 0.7	2.0 ± 1.0	1.9 ± 0.9
Patient Global Assessment (PGA)	3.4 ± 1.0	1.8 ± 0.9	1.8 ± 0.9
POEM (mean; SD)	19.3 ± 6.4	8.8 ± 5.9 p < 0.001*	7.9 ± 5.9
NRS pruritus (mean; SD)	6.4 ± 2.2	2.7 ± 2.1 p < 0.001*	2.8 ± 2.0
NRS sleeping problems (mean; SD)	5.4 ± 3.0	1.5 ± 2.1 p < 0.001*	1.5 ± 2.1
DLQI (mean; SD)	12.4 ± 6.7	4.4 ± 5.2 p < 0.001*	4.2 ± 4.5
Level of disease control within past 12 weeks - well controlled weeks - completely controlled weeks	3.3 ± 3.1 0.6 ± 13	8.5 ± 3.7 p < 0.001* 5.7 ± 4.5 p < 0.001*	9.5 ± 3.2 6.3 ± 4.5
Dryness of skin (mean; SD) - oSCORAD (intensity) - POEM, question 7	2.0 ± 0.9 3.4 ± 1.1	1.1 ± 0.8 p < 0.001* 2.0 ± 1.5 p < 0.001*	1.2 ± 0.8 2.0 ± 1.4

* p-value for paired t-test, baseline vs. 1st follow-up visit

** paired t-test, 1st vs. 2nd follow-up visit: no significant differences;

SD: Standard deviation

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