SHORT COMMUNICATION

Treatment of Moderate-to-severe Atopic Dermatitis with Upadacitinib: Results from an Interim Analysis of the TREATgermany Registry

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The JAK1 inhibitor upadacitinib substantially extended the treatment options of moderate-to-severe AD. In clinical trials, upadacitinib demonstrated high efficacy, particularly at 30 mg daily, with rapid improvements within 12–16 weeks (1, 2). Unlike targeted biologics, upadacitinib offers broader immunomodulation but requires careful monitoring due to potential risks, especially in older patients or those with cardiovascular or malignancy risk factors (3–5). Common side effects include acne-like eruptions, respiratory infections, and viral skin infections (6). Evidence for upadacitinib generated in the context of everyday clinical care is limited. Initial studies suggest strong effectiveness and safety, even in difficult-to-treat cases (7, 8).

MATERIALS AND METHODS

The TREATgermany registry is investigating its use in daily practice. TREATgermany is one of the largest AD registries worldwide, currently comprising > 2,000 adult patients with moderate-to-severe AD eligible for or receiving systemic therapy (9, 10). Here, all adult patients enrolled in the registry who received upadacitinib until December 2023 were included. Alongside demographics, disease history, and adverse events, prospective patient and physician assessments of disease activity using validated instruments were analysed (10, 11).

RESULTS

A total of 97 patients (mean age 36.7 ± 14.2 years, 42.3% female) who had initiated upadacitinib during registry observation were eligible for this analysis (Fig. S1). Fifty-two of the 97 upadacitinib-treated patients (53.6%) displayed at least 1 of the risk factors defined by the Pharmacovigilance Risk Assessment Committee (PRAC) (12). Twenty-three (23.7%) were active smokers and 20 (20.6%) have smoked in the past. Four patients were older than 64 years and 18 patients had relevant comorbidities (hypertension $n = 17$, cardiac insufficiency $n = 1$). If ex-smokers are omitted, still 37 (38.1%) patients met at least 1 risk factor. The majority of patients treated with upadacitinib (70.1%, $n = 68$) had previously received other systemic therapies and 31 transitioned from a previous ongoing systemic therapy without wash-out.

Of the 97 patients with an upadacitinib initiation registry visit, 36 patients (37.1%) initially received 15 mg daily, while 61 (62.9%) started with 30 mg (**Fig. 1**). Logistic regression revealed that the odds of receiving the lower initial dose was 8 times higher for females ($p = 0.0006$). The odds of receiving a prescription for the lower dose were 84% (6 times) lower for a patient who was treated in a dermatology office compared with a patient being treated in a university special outpatient clinic (hospital) ($p = 0.0041$). There was no significant association of smoking or being an ex-smoker with the lower initial dose of upadacitinib.

Among the 97 patients, 76 (78.4%) had at least 1 follow-up visit under upadacitinib treatment and were eligible for effectiveness analysis (Table SI). For better comparability of the continuous registry data with upadacitinib approval studies, 2 observation periods were defined: 3 months (13 ± 2 weeks, $n = 43$) and 6 months (26 ± 4 weeks, $n = 35$) of therapy (**Table I**).

At month 3, disease severity had improved in the vast majority of patients receiving upadacitinib (Table I). The EASI-50, EASI-75, EASI-90, and EASI-100 response rates were 81%, 63%, 40%, and 12%. An improvement at month 3 was also evident in POEM and DLQI.

The proportion of patients with little or uncontrolled disease (RECAP ≥ 12) decreased from 85.5% at therapy start to 21.4%, and 42.9% of the patients had completely or mostly controlled (RECAP ≤ 5) disease. The number of completely controlled weeks increased from 1.3 ± 2.4 to 6.3 ± 4.7 under upadacitinib treatment. There were also improvements in the symptoms, average skin pain, pruritus, and loss of sleep in the past 3 days as well as peak pruritus (PP-NRS) in the last 24 h, with pruritus being both the highest rated symptom and the symptom with the strongest (absolute) improvement. The proportion of patients who achieved a PP-NRS ≥ 4-point improvement from start was 52.4%. Patient satisfaction with medical treatment improved from 5.5 ± 2.8 to 7.6 ± 2.5.

Across all outcomes, a further improvement at month 6 was achieved compared with month 3 (Table I). Sleep loss reduced

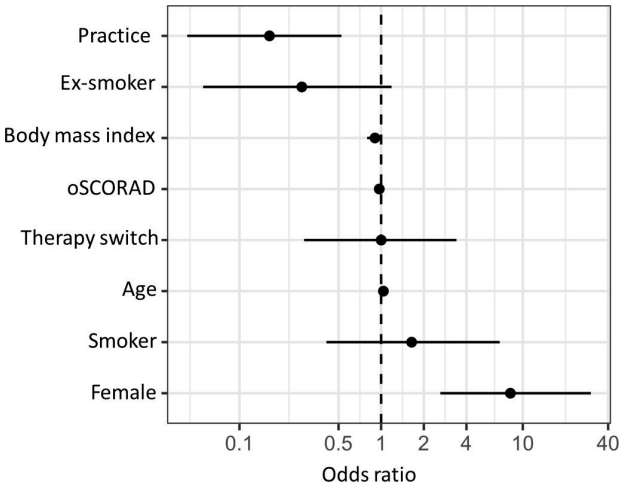

Fig. 1. What influenced the chance of being prescribed the lower initial dose of 15 mg upadacitinib per day? Odds ratio and 95% confidence interval of the variables: study site (doctor's practice/clinic), smoking stopped (within 10 years and more than 10 years), body mass index, oSCORAD at upadacitinib start visit, direct switch to upadacitinib from another systemic therapy, active smoking, biological sex.

Table I. Disease severity at start visit, first follow-up visit, and follow-up visits after 3 months and 6 months as assessed by physicians and patients

Factor	Upadacitinib start visit of the patients with follow-up $n = 76$	Time frames		
		Follow-up visit $n = 76$	Follow-up visit at 3 months $n = 43$	Follow-up visit at 6 months $n = 35$
Physician-reported outcomes				
oSCORAD	43.7±15.2	19.9±13.7	19.3±12.7	17.1±14.3
oSCORAD categories				
Clear = 0–8	0 (0.0%)	16 (21.3%)	9 (21.4%)	11 (32.4%)
Mild = 8–24	4 (5.3%)	38 (50.7%)	22 (52.4%)	15 (44.1%)
Moderate = 24–38	24 (31.6%)	11 (14.7%)	7 (16.7%)	3 (8.8%)
Severe = 38–83	48 (63.2%)	10 (13.3%)	4 (9.5%)	5 (14.7%)
EASI score	17.8±12.4	5.3±7.9	5.1±7.4	3.8±5.8
EASI categories				
Clear = 0	0 (0.0%)	9 (11.8%)	5 (11.6%)	6 (17.6%)
Mild = 0–6	13 (17.1%)	49 (64.5%)	27 (62.8%)	22 (64.7%)
Moderate = 6–23	41 (53.9%)	14 (18.4%)	9 (20.9%)	6 (17.6%)
Severe = 23–72	22 (28.9%)	4 (5.3%)	2 (4.7%)	0 (0.0%)
EASI subscales				
EASI head and neck	1.7±1.2	0.7±0.9	0.7±0.8	0.7±1.0
EASI trunk	5.4±4.3	1.5±2.7	1.4±2.1	1.1±2.0
EASI arms	4.3±2.8	1.3±2.2	1.1±1.7	1.0±2.1
EASI legs	6.4±6.0	1.9±3.4	1.9±3.9	1.0±1.8
EASI response rates				
EASI-50	–	60 (78.9%)	35 (81.4%)	29 (85.3%)
EASI-75	–	50 (65.8%)	27 (62.8%)	24 (70.6%)
EASI-90	–	32 (42.1%)	17 (39.5%)	18 (52.9%)
EASI-100	–	9 (11.8%)	5 (11.6%)	6 (17.6%)
Physicians' satisfaction with treatment	4.2±2.9	7.9±2.3	7.8±2.2	8.3±1.9
Patient-reported outcomes				
DLQI	12.7±7.0	4.5±5.5	5.7±6.4	3.8±5.2
POEM	18.1±7.0	6.7±6.2	7.4±6.5	5.9±5.4
Fatigue score	3.7±1.7	3.1±1.5	3.0±1.5	2.9±1.3
CESD score	16.4±10.5	11.9±9.3	13.0±10.4	10.8±8.0
RECAP	17.2±5.5	6.8±6.4	7.6±6.8	5.1±5.2
Good controlled weeks	3.3±3.5	8.4±3.7	8.2±3.8	9.5±3.0
Completely controlled weeks	1.3±2.4	6.6±4.5	6.3±4.7	7.9±4.1
Skin pain last 3 days	4.1±2.6	1.7±1.9	1.9±2.1	1.3±1.9
Pruritus last 3 days	6.4±2.5	2.7±2.2	2.9±2.4	2.2±1.8
Sleep loss last 3 days	5.2±3.3	1.7±2.7	1.7±2.8	1.2±2.0
Peak pruritus last 24 hrs	6.0±2.8	2.4±2.4	2.6±2.5	2.1±2.3
BSA	18.5±17.1	4.8±8.0	5.6±8.8	7.3±17.8
Patients' satisfaction with medical treatment	5.5±2.8	8.1±2.4	7.6±2.5	8.4±2.0
Patients' satisfaction with medical care	7.5±2.5	8.5±2.1	8.6±2.2	8.6±2.1

from 5.2±3.3 to 1.2±2.0. Patient satisfaction with medical treatment improved from 5.5±2.8 to 8.4±2.0. The proportion of patients who achieved a PP-NRS ≥ 4-point improvement from start was 60.6% at month 6. Likewise, 57.6% had completely or mostly controlled (RECAP ≤ 5) disease.

Safety data were analysed for all 76 patients with at least 1 follow-up visit while on upadacitinib therapy. A total of 15 adverse events (AEs) in 12 of these patients (15.8%) were reported. Most frequently reported AE were acne/acneiform skin lesions (5.2%, $n = 4$) and headache (2.6%, $n = 2$). Hyperlipidaemia, increase in liver values, worsening of atopic prurigo, herpes zoster, superinfection of the hand, impetigo contagiosa, and nausea/vomiting were each reported once.

The following AEs were reported once, but the causality was assessed as unlikely by the physician: recurrent styes, and fever. An additional 3 patients discontinued upadacitinib before the follow-up visit. In 2 of these patients an AE leading to treatment discontinuation was reported: 1 patient developed granulocytopenia, and another patient had recurrent cystitis and weight gain.

DISCUSSION

This first analysis of clinical effectiveness, safety, and utilization patterns of upadacitinib from the TREATgermany registry suggests robust clinical effectiveness with improvements in both objective and subjective disease activity measures, and favourable tolerability over 6 months of treatment. Clinical effectiveness was slightly lower than the efficacy observed in clinical trials, which may be explained by differences in the baseline characteristics of the study cohorts, divergent inclusion criteria, and no wash-out period for topical treatments prior to upadacitinib initiation. To reflect daily practice, patients with direct changes of systemic therapy were included in the analysis, which is another possible reason for lower EASI and itch response rates. The discontinuation rate (3 of 79 patients; 3.8%) until first follow-up visit was lower than in a recent small difficult-to-treat routine patient cohort (7). The proportion of patients with little or uncontrolled disease (RECAP ≥ 12) decreased from 85.5% at therapy start to 21.4% at month 3 and 18.2% at month 6. At months 3 and 6, 42.9% and 57.6% had completely or mostly controlled (RECAP ≤ 5) disease.

The majority of patients who received upadacitinib in TREATgermany had undergone other systemic treatments for AD in the past. This included dupilumab, which had been used in 34% of the patients prior to upadacitinib

treatment. Upadacitinib-treated patients less often had comorbid asthma and rhinitis. A potential benefit of upadacitinib on comorbid respiratory disease is insufficiently investigated thus far, but limited data exist on the benefit of upadacitinib on atopic comorbidities (13). In total, 46.2% of patients treated with upadacitinib were current or past long-term smokers, i.e., had a risk factor for serious side effects with JAK inhibitors according to PRAC (14). Of those, 69.8% were initiated on a high upadacitinib dose. However, the majority of patients (75 of 97) were started on upadacitinib prior to the release of the PRAC recommendations in Germany, and up to now trial data have not indicated increased incidence rates for MACE, venous thromboembolism (VTE), and malignancies with JAK inhibitor use in AD (15).

In the patient population studied here for up to 6 months of treatment no SAE and a rather low number of AEs were reported. There were no reports of MACE, VTE, or malignancies. In conclusion, our data suggest that upadacitinib treatment is effective and well tolerated in adult patients with moderate-to-severe AD. Limitations of the presented analyses are the rather low sample size and short observation period. Future longer-term observations from TREATgermany and other registries will provide important additional insights into potential rare AEs, and how the PRAC recommendations impact routine use of JAK inhibitors in AD.

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