Treatment with alitretinoin in patients taking part in a tertiary individual prevention program for work-related skin diseases

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Abstract

Background: Patients taking part in a tertiary individual prevention program (TIP) for work-related skin diseases frequently have chronic hand eczema (HE) for which alitretinoin is a treatment option.

Objective: To investigate treatment with alitretinoin before and during the TIP and related factors.

Methods: Data of 1614 patients taking part in the TIP between January 2015 and December 2019 were analyzed retrospectively.

Results: Three hundred forty-eight patients (21.6%) reported treatment with alitretinoin prior to the TIP showing an increase over time, particularly in men. In 45 patients (2.8%), alitretinoin treatment was initiated during the TIP. Treatment with alitretinoin was significantly less common among female than male patients, both prior to (P < .001) and during the TIP (P = .015). Female patients who had received alitretinoin in the past were significantly older than the other female patients (P < .001). Among patients treated with alitretinoin prior to the TIP, women had a significantly higher disease severity at admission than men (P = .007).

Conclusions: About twenty percent of patients reported treatment with alitretinoin prior to the TIP. The data indicate that treatment of female TIP patients with alitretinoin is less frequent than among male patients and depends on age and disease severity.

KEYWORDS
alitretinoin, contact dermatitis, hand eczema, hyperkeratotic, occupational, prevention, tobacco smoking, vesicular, work-related

INTRODUCTION

Hand eczema (HE) is a common disease with a 1-year prevalence of about 10% in the general population.1 Moreover, it is the most common occupational or work-related skin disease.2 It is mainly caused by irritant or allergic contact dermatitis or atopic dermatitis. Usually, it is a multifactorial disease with varying clinical patterns and severity, which is often accompanied by considerable impairment of quality of life.3,4 In addition, socioeconomic costs associated with chronic HE and especially occupational or work-related HE are high and primarily related to treatment, prolonged work absenteeism, job change, and unemployment.5,6

A chronic course that has been defined as duration of HE for more than 3 months or two relapses within a year is frequent.4 In Germany, alitretinoin (9-cis-retinoic acid) has been licensed since 2008 for adults with severe chronic HE who are refractory to topical treatment
with potent steroids. Alitretinoin is a derivative of vitamin A that binds to both retinoic acid receptors (RARs) and retinoid X receptors (RXRs). The exact mechanism of action is unclear. Studies indicate immunomodulatory and anti-inflammatory effects of alitretinoin, including inhibition of cytokine synthesis, leucocyte recruitment, and T-cell activation by antigen-presenting cells. A dose of 30 mg once daily is recommended as it is associated with a faster and higher response than a daily dose of 10 mg, which is used in patients with pre-existing health concerns or intolerable adverse events relative to the higher dose. The usual treatment duration lasts 12 to 24 weeks depending on tolerability and response. Treatment is ceased if no response is observed until 12 weeks of treatment or if healing occurs prior to a treatment duration of 24 weeks. However, extended treatment beyond 6 months may be beneficial in early non-responders and in patients who experience some, but not sufficient improvements.

In case of a good response to a first treatment, re-treatment is an option if the disease worsens or recurs. Due to its teratogenicity, alitretinoin is strictly contraindicated during pregnancy. Treatment of women of child-bearing age should therefore be initiated only after exclusion of pregnancy twice in a 4-week interval. During treatment and until 4 weeks after cessation of treatment, strict adherence to pregnancy-prevention measures and regular pregnancy tests are mandatory.

In Germany, patients with severe work-related skin diseases that are refractory to outpatient treatment and preventive measures are invited to take part in an inpatient/outpatient tertiary prevention program (TIP) financed by the statutory accident insurance. The TIP has been described in detail elsewhere. Briefly, it consists of a 3-week inpatient intervention phase in a specialized center including diagnostics, treatment, patient education, and individual selection of adequate personal protective equipment, which is followed by a 3-week outpatient phase of absence from work under the guidance of a local dermatologist at the patient's hometown before returning to work. The majority of TIP patients (>90%) have severe chronic HE and thus are eligible for treatment with alitretinoin. However, not much is known about alitretinoin treatment in patients with chronic work-related skin diseases in Germany, and if the patient's gender may affect treatment decisions. Therefore, the objective of this retrospective study was to collect data on treatment with alitretinoin prior to or during the TIP, with a special focus on gender-specific differences.

2 METHODS

2.1 Patients

Data of patients who took part in the TIP at the Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation (iDerm) at the University of Osnabrück, Germany, between January 2015 and December 2019 were analyzed retrospectively. The patients had given informed consent for use of the routinely obtained data during the TIP for continuous quality management assessments, which also includes scientific analyses of anonymized data. In the case of minors (<18 years of age) informed consent was obtained from their legal representatives. Apart from obtaining a detailed patient history, a thorough diagnostic work-up of the presented skin disease was done during the TIP, including patch testing. A combination of different final diagnoses was possible. At admission and dismissal, a dermatologist used the validated Osnabrueck Hand Eczema Severity Index (OHSI) to assess the severity of the disease if the hands were affected. A value >0 in the OHSI subcategory for vesicles was considered an indicator for vesicular HE. Data including age, gender, and treatment with alitretinoin were available for all patients. More detailed data analyses were done of patients who reported treatment with alitretinoin prior to the TIP (group A). Moreover, data from patients in which treatment with alitretinoin was initiated during the TIP (group B) and patients in which treatment was initially considered, but not started during the TIP (group C), were compared. There was an overlap of patients in groups A and B as well as in groups A and C.

2.2 Data analysis

Statistical analyses were conducted with SPSS, Version 27.0 (IBM Corp., Armonk, New York). Differences for categorical variables were assessed using the Pearson's chi-square (χ²) test. Fisher's exact test was applied if at least one expected value under independence was <5. To analyze differences for continuous variables, uni-factorial analysis of variance was used, whereas the Mann–Whitney U test was applied for the OHSI. Differences were considered significant if the P value was <.05.

3 RESULTS

3.1 Demographic data of all patients

Between January 2015 and December 2019, a total of 1614 patients from across Germany took part in the TIP at the iDerm in Osnabrück. During this period of time, 22 patients (1.4%) participated more than once in the TIP. Of these, only data collected during the last TIP were included in the analyses. About half of the patients were female (n = 826, 51.2%). The mean age ± standard deviation (SD) and range was 47.09 ± 11.82 (17-73) years (Table 1).

3.2 Characteristics of patients who reported treatment with alitretinoin prior to the TIP

Treatment with alitretinoin prior to the TIP was reported by 348 patients (21.6%) (group A) (Tables 1 and 2). The annual rate increased from 17.8% in 2015 to 24.2% in 2019 (Table 2). A significantly higher share of men (n = 202, 25.6%) than women (n = 146, 17.7%, P < .001) reported treatment with alitretinoin prior to the TIP. Apart from 2016, the rate of self-reported treatment with alitretinoin before the TIP was always higher among male than female patients,
TABLE 1  Age of patients who reported or negated treatment with alitretinoin prior to the tertiary individual prevention program (TIP)

|                      | All TIP patients | Alitretinoin treatment prior to the TIP | No alitretinoin treatment prior to the TIP | P value |
|----------------------|------------------|----------------------------------------|------------------------------------------|---------|
| Total                | n = 1614         | n = 348                                | n = 1266                                 |         |
| Age (y), mean ± SD   |                  | 47.09 ± 11.82 (17-73)                  | 49.78 ± 10.24 (20-68)                    | <.001   |
|                      |                  | 46.35 ± 12.12 (17-73)                  |                                         |         |
| Men                  | n = 788 (48.8%)  | n = 202                                | n = 586                                  |         |
| Age (y), mean ± SD   |                  | 47.71 ± 11.20 (17-73)                  | 49.43 ± 10.09 (20-68)                    | .011    |
|                      |                  | 47.12 ± 11.51 (20-68)                  |                                         |         |
| Women                | n = 826 (51.2%)  | n = 146                                | n = 680                                  |         |
| Age (y), mean ± SD   |                  | 46.49 ± 12.37 (17-65)                  | 50.27 ± 10.45 (22-65)                    | <.001   |
|                      |                  | 45.68 ± 12.60 (17-65)                  |                                         |         |

Note: Bold values indicates significant p values.
Abbreviation: TIP, tertiary individual prevention program.

TABLE 2  Annual rate of patients who reported treatment with alitretinoin prior to the tertiary individual prevention program (TIP)

|                      | Total n/n total (%) | Men n/n total (%) | Women n/n total (%) | P value |
|----------------------|---------------------|------------------|---------------------|---------|
| 2015                 | 48/269 (17.8)       | 29/124 (23.4)    | 19/145 (13.1)       | .028    |
| 2016                 | 59/274 (21.5)       | 29/136 (21.3)    | 30/138 (21.7)       | .933    |
| 2017                 | 72/338 (21.3)       | 42/170 (24.7)    | 30/168 (17.9)       | .124    |
| 2018                 | 80/365 (21.9)       | 50/189 (26.5)    | 30/176 (17.0)       | .030    |
| 2019                 | 89/368 (24.2)       | 52/169 (30.8)    | 37/199 (18.6)       | .007    |
| 2015-2019            | 348/1614 (21.6)     | 202/788 (25.6)   | 146/826 (17.7)      | <.001   |

Note: Bold values indicates significant p values.

with significant differences in 2015 (P = .028), 2018 (P = .030), and 2019 (P = .007). In men, the annual rate increased from 23.4% in 2015 to 30.8% in 2019. After an increase from 13.1% in 2015 to 21.7% in 2016, the rate of self-reported treatment with alitretinoin in the past ranged between 17% and 19% in female patients. As shown in Table 1, the 348 patients who reported treatment with alitretinoin prior to the TIP, were significantly older than the other 1266 patients (mean age ± SD: 49.78 ± 10.24 years vs 46.35 ± 12.12 years, P < .001). Particularly, the 146 women reporting treatment with alitretinoin in the past were significantly older than the 680 female patients who did not (mean age ± SD: 50.27 ± 10.45 years vs 45.68 ± 12.60 years, P < .001).

Characteristics of the 348 patients reporting treatment with alitretinoin in the past are presented in Table 3. The most common professions were healthcare workers (n = 89, 25.6%), metal workers (n = 63, 18.1%), construction workers (n = 34, 9.8%), food handlers (n = 23, 6.6%), and cleaners (n = 18, 5.2%). Tobacco smoking was reported by 140 patients (40.2%). The rate of self-reported tobacco smoking was significantly higher among women than men (47.9% vs 34.7%, P = .013). HE was diagnosed in most patients (n = 303, 87.1%). The most frequent subtypes were atopic HE (n = 193, 63.7%) and irritant contact dermatitis of the hands (n = 151, 49.8%). Hyperkeratotic HE was diagnosed significantly more often in men than in women (31.5% vs 16.4%, P = .001). Based on the OHSI, 120 patients (39.6%) had vesicular HE on admission, without significant differences between men and women. It was more frequent among smokers than non-smokers (45.7% vs 26.9%, P < .001) as well as among patients with atopic HE than those without (52.3% vs 12.3%, P < .001). The most common diagnoses in patients without HE, other than skin lesions of the hands, were palmar psoriasis (n = 27, 7.8%) and palmar pustulosis (n = 10, 2.9%). The mean OHSI at admission was 6.6 ± 3.2 (n = 346). It was significantly higher in women than in men (7.1 ± 3.2 vs 6.2 ± 3.1, P = .007). Some patients (n = 62, 17.8%) reported systemic treatment with other drugs than alitretinoin prior to the TIP, including acitretin (n = 31, 8.9%), cyclosporine (n = 21, 6.0%), methotrexate (n = 16, 4.6%), or fumaric acid (n = 8, 2.3%).

3.3  Self-reported data related to treatment with alitretinoin prior to the TIP in patients with HE

The self-reported data related to treatment with alitretinoin in the past was analyzed in all patients in group A with HE (n = 303). The results are presented in Table S1. The majority reported treatment with a daily dose of 30 mg only (n = 143, 47.2%). In 85 patients (28.1%) the dose was not documented. The mean number of continuous treatment months with at least 1 day of treatment was 6.40 ± 7.60 (n = 274), with a broad range of 1-63 months. In patients reporting more than one cycle of alitretinoin treatment with several weeks of interruption in-between, only the longest treatment duration was included in the analysis. In 111 of 274 patients (40.5%), the treatment lasted ≤3 months. Most of them (n = 62) reported only 1 month with at least 1 day of treatment indicating an early stop of treatment in
about one quarter of patients. Seventy-eight patients (28.5%) reported treatment for 4-6 months. Treatment >6 months was reported by 31.0% of patients, but treatment >12 months was only rarely (7.7%) reported. Data on number of treatment cycles were available for 285 patients. Most of them reported only one treatment cycle (n = 247, 86.6%).

Adverse events related to treatment with alitretinoin were reported by 142 of 303 patients (46.9%). The most frequent were headache (n = 41, 13.5%), hyperlipidemia (n = 30, 9.9%), and gastrointestinal complaints (n = 23, 7.6%). A significantly higher share of patients who reported treatment with alitretinoin for ≤1 month compared to those who reported treatment for >1 month indicated adverse events (39/62, 62.9% vs 90/212, 42.5%, P = .005) and among adverse events, significantly more often headache (17/62, 27.4% vs 23/212, 10.8%, P = .001).

In 100 patients with HE, no information on the course of the disease during treatment with alitretinoin prior to the TIP was available from the files (33.0%) (Table S1). Twenty-four (7.9%) patients reported complete healing, whereas improvement was reported by 74 (24.4%) patients. Thus healing or improvement were reported by 98 patients (32.3%), which equals 48.3% of all 203 patients of which information on the course of the disease was available. About half of the women and half of the men in this group of 203 patients reported improvement or healing of the disease.

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The 98 patients with self-reported positive response to the treatment with alitretinoin were compared with the 105 patients reporting no response or worsening of the disease (Table S2). The duration of the disease prior to the TIP and the mean age were similar in both groups. Nearly 60% of tobacco smokers claimed no response or worsening of the disease. This rate was lower among non-smokers (47.6%, P = .134). The disease severity at admission based on the OHSI was significantly higher in patients reporting no response or worsening of the disease during treatment with alitretinoin than in patients reporting a positive response (7.03 ± 3.20 vs 6.03 ± 3.14, P = .027).

### Table 3: Characteristics of patients reporting treatment with alitretinoin prior to the tertiary individual prevention program (TIP)

|                      | Total n = 348 | Men n = 202 (58.0%) | Women n = 146 (42.0%) | P value |
|----------------------|---------------|---------------------|------------------------|---------|
| Age (y), mean ± SD   | 49.78 ± 10.24 | 49.43 ± 10.09       | 50.27 ± 10.45          | .450    |
| Tobacco smoker, n (%)| 140 (40.2)    | 70 (34.7)           | 70 (47.9)              | .013    |
| Duration of skin disease before TIP (y), mean ± SD | N = 313 | n = 183 | n = 130 | .350 |
|                      | 8.93 ± 8.50   | 9.31 ± 8.46         | 8.39 ± 8.56            |         |
| Hand eczema, n (%)   | 303 (87.1)    | 181 (89.6)          | 122 (83.6)             | .097    |
| Subtype of hand eczema, n (%) |         |                    |                       |         |
| Atopic               | 193 (63.7)    | 105 (58.0)          | 88 (72.1)              | .124    |
| Irritant contact dermatitis | 151 (49.8) | 81 (44.8) | 70 (57.4) | .145 |
| Allergic contact dermatitis | 25 (8.3) | 15 (8.3) | 10 (8.2) | .837 |
| Hyperkeratotic       | 77 (25.4)     | 57 (31.5)           | 20 (16.4)              | .001    |
| Vesicular hand eczema, n (%) | 120 (39.6) | 68 (37.6) | 52 (42.6) | .705 |
| Other diagnoses hands, n (%) |               |                     |                       |         |
| Palmar psoriasis     | 27 (7.8)      | 14 (6.9)            | 13 (8.9)               | .497    |
| Palmar pustulosis    | 10 (2.9)      | 2 (1.0)             | 8 (5.5)                | .013    |
| Foot eczema, n (%)   | 65 (18.7)     | 44 (21.8)           | 21 (14.5)              | .081    |
| OHSI at admission, mean ± SD | n = 346 | n = 201 | n = 145 | .007 |
|                      | 6.55 ± 3.18   | 6.15 ± 3.10         | 7.11 ± 3.21            |         |
| Systemic treatment other than alitretinoin in the past, n (%) | 62 (17.8) | 42 (20.8) | 20 (13.7) | .088 |
| Other systemic treatment in the pastb, n/ntotal (%) |         |                     |                       |         |
| Acitretin            | 31 (8.9)      | 21 (10.4)           | 10 (6.8)               | .252    |
| Cyclosporine         | 21 (6.0)      | 15 (7.4)            | 6 (4.1)                | .205    |
| Methotrexate         | 16 (4.6)      | 11 (5.4)            | 5 (3.4)                | .374    |
| Fumaric acid         | 8 (2.3)       | 5 (2.5)             | 3 (2.1)                | 1.000   |

Note: Bold values indicates significant p values.

Abbreviations: OHSI, Osnabrueck Hand Eczema Severity Index; SD, standard deviation; TIP, tertiary individual prevention program.

aBased on OHSI.
bMore than one possible.
fewer patients with vesicular HE (40.0% vs 54.2%, \(P = .045\)) or atopic HE (42.9% vs 58.6%, \(P = .033\)) reported improvement or healing during treatment with alitretinoin. In contrast, a self-reported positive response was significantly more common in patients with hyperkeratotic HE than in those without (64.7% vs 42.8%, \(P = .007\)).

### 3.4 Treatment with alitretinoin initiated during the TIP

In 45 patients (2.8%), treatment with alitretinoin was initiated during the TIP between January 2015 and December 2019 (group B) (Table 4).

Two thirds of them were men \((n = 30, 66.7\%)\), which equals 3.8% of all 788 male TIP patients. The share of female TIP patients in which treatment with alitretinoin was started during the TIP was significantly lower \((n = 15/826, 1.8\%, \ P = .015\)). In another 208 patients (12.9%), treatment with alitretinoin was considered during the TIP, but not initiated until dismissal (group C). There were significantly fewer women in group B than in group C \((n = 15, 33.3\% \text{ vs } n = 112, 53.8\%, \ P = .013\). The mean age in group B \((52.21 \pm 10.02 \text{ years})\) was higher than in group C \((48.55 \pm 11.35 \text{ years}, \ P = .05)\). Within group B, women in which treatment with alitretinoin was started were older \((55.07 \pm 7.02\text{ years}, \text{range: }37-65\text{ years})\) than men \((49.09 \pm 11.64\text{ years}, \text{range: }21-65\text{ years}, \ P = .573)\). The severity of the disease according to the OHSI was significantly higher in group B than group C, both at admission \((8.91 \pm 3.47\text{ vs }7.43 \pm 3.32, \ P = .014)\) and even more pronounced at dismissal \((5.88 \pm 2.48\text{ vs }4.20 \pm 2.13, \ P < .001)\). The main reasons for not commencing therapy with alitretinoin were marked improvement of skin disease during the TIP \((n = 84, 40.4\%)\) or that the patient declined the treatment \((n = 60, 28.8\%)\). Other reasons were hyperlipidemia \((n = 21, 10.1\%)\) or allergies against peanut or soy \((n = 9, 4.3\%)\). In two patients (1.0%), treatment with alitretinoin was considered problematic because of not sufficiently controlled depression.

Other rare reasons were, for example, history of intracranial hypertension, current pregnancy plans, inadequate contraceptive measures, or liver cirrhosis.

| TABLE 4 Comparison of patients in which treatment with alitretinoin was initiated during the tertiary individual prevention program (TIP) (group B) with patients in which treatment with alitretinoin was considered but not initiated during the TIP (group C) |
|-------------------------------|-------------------------------|-------------------|
|                                | Group B \((n = 45)\)          | Group C \((n = 208)\) | \(P\) value |
| Women, \(n(\%)\)               | 15 \((33.3)\)                 | 112 \((53.8)\)      | .013        |
| Age \((y)\) (total), mean ± SD (range) | 52.16 ± 10.02 \((21-65)\)   | 48.55 ± 11.35 \((17-64)\) | .050        |
| Age \((y)\) (men), mean ± SD (range) | 55.07 ± 7.02 \((37-65)\)   | 49.09 ± 11.64 \((17-64)\) | .055        |
| Age \((y)\) (women), mean ± SD (range) | 50.70 ± 11.04 \((21-65)\) | 47.93 ± 11.03 \((21-64)\) | .232        |
| Tobacco smokers, \(n(\%)\)     | 21 \((46.7)\)                | 84 \((40.4)\)       | .438        |
| Hand eczema, \(n(\%)\)         | 45 \((100)\)                 | 196 \((94.2)\)      | .133        |
| Duration of skin disease prior to TIP \((y)\), mean ± SD | \(n = 39\) 8.69 ± 8.82 | \(n = 193\) 8.83 ± 9.24 | .938        |
| OHSI at admission, mean ± SD   | 8.91 ± 3.47                   | 7.43 ± 3.32         | .014        |
| OHSI at dismissal, mean ± SD   | \(n = 42\) 5.88 ± 2.48       | \(n = 206\) 4.20 ± 2.13 | <.001       |
| Systemic therapy prior to TIP, \(n(\%)\) | 11 \((24.4)\) 47 \((22.6)\) | .789        |
| Type of systemic therapy prior to TIP, \(n(\%)\) | 10 \((22.2)\) 40 \((19.2)\) | .648        |
| Atopic                         | 24 \((53.3)\)                 | 102 \((48.1)\)      | .601        |
| Irritant contact dermatitis    | 33 \((73.3)\)                 | 138 \((70.4)\)      | .364        |
| Allergic contact dermatitis   | 5 \((11.1)\)                  | 18 \((9.2)\)        | .573        |
| Hyperkeratotic                 | 10 \((22.2)\)                 | 50 \((25.5)\)       | .795        |
| Vesicular hand eczeem\(a\), \(n(\%)\) | 27 \((60.0)\) 96 \((49.0)\) | .092        |
| OHSI at admission, mean ± SD   | 8.91 ± 3.47                   | 7.43 ± 3.32         | .014        |
| OHSI at dismissal, mean ± SD   | \(n = 42\) 5.88 ± 2.48       | \(n = 206\) 4.20 ± 2.13 | <.001       |
| Note: Bold values indicates significant \(p\) values. Abbreviations: OHSI, Osnabrueck Hand Eczema Severity Index; SD, standard deviation; TIP, tertiary individual prevention program. *Based on OHSI. **More than one possible.
To the best of our knowledge, this is the first real-life study presenting detailed data on treatment with alitretinoin in a large cohort of patients with severe work-related skin diseases. Alitretinoin is the only systemic drug licensed in Germany for systemic treatment of severe and chronic HE. Treatment is reimbursed by the German statutory accident insurances if an occupational cause of the disease is likely. The majority of TIP patients have severe and chronic HE refractory to outpatient measures. Therefore, it is not surprising that about 20% of patients in the study period reported treatment with alitretinoin prior to the TIP. This rate has increased over the years, particularly in male patients. Not much has been published about provision of treatment with alitretinoin in patients with HE. A German registry study revealed that 35.3% of 1163 patients with chronic HE had received systemic therapy (including corticosteroids, but excluding antihistamines) in the year prior to inclusion in the registry, which was established in 2009. At the 5-year follow-up, 39.0% of the patients reported treatment with alitretinoin, acitretin, or methotrexate since inclusion in the registry. In a cross-sectional questionnaire study from Denmark, only 10.0% of 1565 participants with chronic recognized occupational HE reported to have received systemic therapy. Even though this share was slightly higher in patients with self-reported moderate-to-severe HE (13.3%), the overall lower rate in the Danish study may indicate differences in the study populations as well as national legal and medical systems.

About 90% of patients with self-reported alitretinoin treatment prior to the TIP had HE and had a mean disease duration of nearly 9 years. Significantly more men than women reported treatment with alitretinoin in the past. In addition, these patients were significantly older than the other TIP patients. Also in the Danish study, systemic treatment of chronic occupational HE was associated with higher age. This is likely related to the fact that treatment with alitretinoin is usually started in patients with longstanding disease that had previously not responded sufficiently to topical therapies and possibly reluctance among physicians to initiate systemic treatment in younger age groups. The teratogenicity of alitretinoin hampers especially treatment of women of childbearing age, which probably explains that particularly women who reported alitretinoin treatment prior to the TIP were significantly older than the other female TIP patients. A current desire to have children is probably not the only reason for the lower rate of treatment with alitretinoin in young women. Female patients of childbearing age might also be deterred by the teratogenicity of the drug or the efforts needed for strict contraception. Another barrier might be the higher efforts required by the physician with regard to provision of sufficient information about teratogenicity, its documentation, and related fear of malpractice. Overall, the data indicate that particularly young female patients with chronic HE are less likely to receive treatment with alitretinoin compared to their male counterparts in the same age group, which may be considered a disadvantage in provision of care.

The severity of the disease at admission according to the OHSI was particularly high in female patients with self-reported alitretinoin treatment in the past (7.11), which was significantly higher than the OHSI of men who indicated previous alitretinoin treatment (6.15). This suggests that men receive treatment with alitretinoin in already less severe cases than women. The related reasons could be similar to the ones discussed for the higher age of female patients reporting treatment with alitretinoin. A significantly higher share of tobacco smokers was found among women than among men with self-reported alitretinoin treatment in the past. Previously, it was shown that HE in TIP patients is more severe and persistent in tobacco smokers than non-smokers. It could be speculated that female tobacco smokers are more likely to be treated with alitretinoin as they may present with more severe and persistent disease than female non-smokers.

For more detailed analysis, we focused on TIP patients with HE who indicated treatment with alitretinoin in the past. About 50% of them reported adverse events related to the treatment. This rate was similar to some observational real-life studies in HE patients showing rates of 39% and 65.3%, but higher than the rate of 23% in the study by Diepgen et al. The reported adverse events correspond well with published data and were mainly headache, hyperlipidemia, and gastrointestinal complaints. About one quarter of patients who provided information regarding the duration of treatment with alitretinoin reported that the treatment did not last longer than 1 month, indicating an early stop of treatment, which may have been related to adverse events as treatment for ≤1 month was significantly associated with reporting of adverse events, in particular, headache. However, other reasons such as lack of adherence are possible. Self-reported information regarding the efficacy of treatment with alitretinoin in the past was available for 203 patients with HE. Of these, nearly 50% reported a positive response with either improvement or healing. The self-reported data are difficult to compare with the results of other studies using standardized physician-based assessment tools. But it is interesting to note that observational, real-life studies in patients with chronic HE treated with alitretinoin showed a Physician Global Assessment (PGA) response of “clear” or “almost clear” in 57%, 46.6%, and 40.9% of patients, respectively. In the study by Dirschka et al, 63.9% of patients were classified as at least partial responders, with ratings of “clear”, “almost clear,” or “mild disease.” A lower response rate in our cohort could be related to retrospective self-reporting, which may be partially incorrect and a selection bias as participation in the TIP is specifically offered to patients with severe skin disease refractory to previous outpatient treatments. The majority of patients reported treatment with alitretinoin for 4 to 6 months and received only one treatment cycle. However, rarely treatment for more than 9 months or more than one treatment cycle was reported, which could be beneficial in some patients as published previously.

A good response to alitretinoin was particularly reported by patients with hyperkeratotic HE, whereas no response or worsening was more commonly reported by patients with vesicular HE. This corresponds well with published data on a higher efficacy of alitretinoin in hyperkeratotic HE than in vesicular HE. In addition, patients
with atopic HE significantly more often indicated treatment failure, which might be related to the significantly higher prevalence of vesicular HE among these patients as reported previously. An atopic HE component was diagnosed in about 64.0% of patients reporting treatment with alitretinoin prior to the TIP. This was the most common HE component in these patients and much higher than the rate (55.0%) found among 1788 TIP patients participating in a previous multicenter study. This might be due to a higher severity and chronicity of atopic HE leading to treatment with alitretinoin. Only in 45 patients (2.8%), treatment with alitretinoin was initiated during the TIP. A likely explanation is that a sufficient disease improvement was achieved in most patients during the 3 weeks of inpatient treatment combined with absence from work as shown previously, rendering initiation of treatment with alitretinoin during the TIP unnecessary. In fact, one reason to participate in the TIP could be to find out if extensive diagnostic work-up, intensified topical treatment, health education, and provision of adequate protective equipment could enable a sustainable disease improvement without the need for systemic treatment. Accordingly, the disease severity at dismissal was significantly higher in patients in which treatment with alitretinoin was commenced during the TIP than in those in which treatment was not started, even though it had been considered initially. This indicates that treatment is initiated mostly in patients with very severe and persistent disease during the TIP. In line with this, improvement of the disease during the TIP and decline by the patient were the main reasons for not starting the therapy. During the TIP, treatment with alitretinoin was also primarily begun in men. The female patients in which treatment with alitretinoin was initiated were older than the male patients treated with alitretinoin. The mean age of the female patients was about 55 years and none of them was younger than 37 years, suggesting that most of them had already reached their menopause. This indicates again, that particularly women in advanced ages are treated with alitretinoin. It should be noted that it is difficult to commence treatment with alitretinoin in women of child-bearing age during the TIP as two pregnancy tests in a 4-week interval are necessary to exclude pregnancy, which could hardly be performed given that the usual duration of the TIP is 3 weeks and only rarely 4 weeks. Therefore, the course and response to topical treatment in these female patients are usually awaited until the end of the TIP. In case of a response, treatment with alitretinoin is more likely put on hold, whereas in men the decision to treat with alitretinoin is often already made in earlier phases of the TIP as waiting for 4 weeks is not necessary to commence treatment as in young women.

5 | LIMITATIONS

This is a retrospective study based on data routinely acquired during the TIP. Very detailed patient’s histories had been taken by experienced physicians. However, the data on treatment with alitretinoin prior to the TIP were self-reported, which may decrease the reliability of the results. This may particularly have affected the information on effectiveness and tolerability of the treatment. Moreover, no standardized survey regarding alitretinoin treatment was performed. Therefore, relevant information was missing for some patients. Nevertheless, despite these limitations, the data correspond well with data from other observational, real-life studies on treatment with alitretinoin.

6 | CONCLUSIONS

In conclusion, TIP patients with work-related skin diseases are frequently treated with alitretinoin prior to the TIP showing an increase over time, particularly in men. Only rarely, treatment with alitretinoin is initiated during the TIP. As suspected, treatment of female TIP patients with alitretinoin is less frequent than treatment of male patients and depends on age and disease severity.

ACKNOWLEDGEMENT

Open access funding enabled and organized by Projekt DEAL

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Lara Obermeyer: Data curation; formal analysis; investigation; writing-original draft; writing-review & editing. Christoph Skudlik: Investigation; resources; writing-review & editing. Sven-Malte John: Investigation; resources; writing-review & editing. Richard Brans: Conceptualization; data curation; formal analysis; investigation; supervision; writing-original draft; writing-review & editing.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Obermeyer L, Skudlik C, John SM. Treatment with alitretinoin in patients taking part in a tertiary individual prevention program for work-related skin diseases. Contact Dermatitis. 2021;1–8. https://doi.org/10.1111/cod.13883