

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

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Abstract

Background: Patients taking part in a tertiary individual prevention programme (TIP) for work-related skin diseases frequently suffer from 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 retrospectively analysed.

Results: 348 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 ($P < .001$) or 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: A high share 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.

Key words: occupational, hand eczema, prevention, alitretinoin, contact dermatitis, hyperkeratotic, vesicular, tobacco smoking, work-related

1. 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 which has been defined as duration of HE for more than three months or two relapses within a year is frequent.⁴ In Germany, alitretinoin (9-*cis*-retinoic acid) is licensed since 2008 for adults with severe chronic HE refractory to topical treatment with potent steroids. Alitretinoin is a derivative of vitamin A which binds to both retinoic acid receptors (RARs) and retinoid X receptors (RXRs).⁷ 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.⁷ 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 related to the higher dose.⁷⁻⁹ The usual treatment duration lasts 12 to 24 weeks depending on tolerability and response.⁷ 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.¹⁰ In case of a good response to a first treatment, re-treatment is an option if the disease worsens or recurs.¹¹ Due to its teratogenicity alitretinoin is strictly contraindicated during pregnancy.⁷ Treatment of women in child-bearing age should therefore only be initiated after exclusion of pregnancy twice in a 4-weeks 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 refractory to outpatient treatment and preventive measures are offered to take part in an inpatient/outpatient tertiary prevention programme (TIP) financed by the statutory accident insurance. The TIP has been described in detail elsewhere.^{12,13} Briefly, it consists of a 3-weeks 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-weeks 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 %) suffers from severe chronic HE¹³ and thus, is 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 retrospectively analysed. 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 case of minors (< 18 years of age) informed consent was obtained from their legal representatives. Apart from taking 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 (OHSEI)^{14,15} to assess the severity of the disease if the hands were affected. A value > 0 in the OHSEI subcategory for vesicles was considered an indicator for vesicular HE. Data of 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 of 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 SPSSTM Version 27.0 (IBM Corp., Armonk, NY, USA). Differences for categorical variables were assessed using the Pearson's chi-squared (χ^2) test. Fisher's exact test was applied if at least one expected value under independence was lower than 5. To analyse differences for continuous variables uni-factorial analysis of variance was

used, while 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, 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) (Table 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, 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 - 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 (40.2%) patients. 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 the vast majority of 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 significantly more often diagnosed in men than women (31.5% vs. 16.4%, $P = .001$). Based on the OHSI, 120 patients (39.6%) suffered from vesicular HE at 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, but 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 analysed in all patients of group A with HE (n=303). The results are presented in Supplemental 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 one day of treatment was 6.40 ± 7.60 (n = 274) with a broad range of 1 - 63 months. In those 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 111/274 patients (40.5%), the treatment lasted ≤ 3 months. Most of them (n = 62) reported only one month with at least one day of treatment indicating an early stop of treatment in about one quarter of patients. 78 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 of 285 patients. Most of them reported only one treatment cycle (n = 247, 86.6%). Adverse events related to treatment with alitretinoin were reported by 142/303 patients (46.9%). The most frequent were headache (n = 41, 13.5%), hyperlipidemia (n = 30, 9.9%) und 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%) (Supplemental Table S1). 24

(7.9%) patients reported complete healing, while improvement was reported by 74 (24.4%) patients. Thus, healing or improvement were reported by 98 (32.3%) patients 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. 103 (34.0%) patients reported no improvement and 2 (0.7%) patients claimed worsening of the disease during treatment with alitretinoin in the past.

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 (Supplemental 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 those reporting a positive response (7.03 ± 3.20 vs. 6.03 ± 3.14 , $P = .027$). Significantly less 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 those 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 less women in group B than in group C ($n = 15$, 33.3% vs. $n = 112$, 53.8%, $P = .013$). The mean age in group B (52.21 ± 10.01 years) was higher than in group C (48.55 ± 11.35 years, $P = .05$). Within group B, women in which treatment with alitretinoin was started were older (55.11 ± 7.02 years, range: 37-65 years) than men (50.70 ± 11.04 years, age: 21-65 years, $P = .171$). Women in group B were also older than women in group C (49.09 ± 11.64 years: range 17-64 years, $P = .06$). The severity of the disease according to the OHSI was significantly higher in group B than group C, both at admission (8.91 ± 3.47 vs. 7.43 ± 3.32 , $P = .01$) and even more pronounced at dismissal (5.88 ± 2.48 vs. 4.20 ± 2.13 , $P < .001$). 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 e. g. history of intracranial hypertension, current pregnancy plans, inadequate contraceptive measures, or liver cirrhosis.

4. Discussion

To the best of our knowledge, this is the first real-life study presenting detailed data on treatment with alitretinoin in a big 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 suffer from severe and chronic HE refractory to outpatient measures.¹³ 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 2009.¹⁶ At the 5-year follow-up, 39.0% of the patients reported treatment with alitretinoin, acitretin or methotrexate since inclusion in the registry.¹⁷ 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.¹⁸ 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 suffered from HE and had a mean disease duration of nearly nine 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.¹⁸ This is likely related to the fact that treatment with alitretinoin is usually started in patients with longstanding disease which had previously not sufficiently responded to topical therapies and possibly reluctance among physicians to

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initiate systemic treatment in younger age groups. The teratogenicity of alitretinoin hampers especially treatment of women in 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 in 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 regards 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 of 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 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.¹⁹ 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%²⁰ and 65.3%²¹, but higher than the rate of 23% in the study by Diepgen et al.²² The reported adverse events correspond well with published data and were mainly headache, hyperlipidemia and gastrointestinal complaints.^{7-9,21,22} About one quarter of patients who provided information regarding the duration of treatment with alitretinoin reported that the treatment did not last longer than one 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

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alitretinoin in the past was available of 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 interestingly, observational, real-life studies in patients with chronic HE treated with alitretinoin showed a Physician Global Assessment (PGA) response of 'clear' or 'almost clear' hands in 57%²², 46.6%⁹ and 40.9%²⁰ 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'.⁹ 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 4-6 months and received only one treatment cycle. However, rarely treatment for more than 9 months or more than one treatment cycle were reported which could be beneficial in some patients as published previously.^{10,11}

A good response to alitretinoin was particularly reported by patients with hyperkeratotic HE, while 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.^{8,22} 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 previously reported.²³ 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 multicentre study.¹³ This might be due to a higher severity and chronicity of atopic HE leading to treatment with alitretinoin.²⁴⁻²⁸

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 three weeks of inpatient treatment combined with absence from work as shown previously¹³, 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 initially had been considered. 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 particular women in advanced ages are treated with alitretinoin. It has to 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 as the usual duration of the TIP is three weeks and only rarely 4 weeks. Therefore, the course and response to topical treatment in these female patients is usually awaited until the end of the TIP. In case of a response, treatment with alitretinoin is more likely put on hold, while 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.

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 corresponds well with data from other observational, real-life studies on treatment with alitretinoin.

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 of male patients and depends on age and disease severity.

References

1. Thyssen JP, Johansen JD, Linneberg A, Menne T. The epidemiology of hand eczema in the general population--prevalence and main findings. *Contact Dermatitis*. 2010;62(2):75-87.
2. Diepgen TL. Occupational skin diseases. *J Dtsch Dermatol Ges*. 2012;10(5):297-313; quiz 314-5.
3. Coenraads PJ. Hand eczema is common and multifactorial. *J Invest Dermatol*. 2007;127(7):1568-70.
4. Diepgen TL, Andersen KE, Chosidow O, et al. Guidelines for diagnosis, prevention and treatment of hand eczema. *J Dtsch Dermatol Ges*. 2015;13(1):e1-22.
5. Diepgen TL, Scheidt R, Weisshaar E, John SM, Hieke K. Cost of illness from occupational hand eczema in Germany. *Contact Dermatitis*. 2013;69(2):99-106.
6. Augustin M, Kuessner D, Purwins S, Hieke K, Posthumus J, Diepgen TL. Cost-of-illness of patients with chronic hand eczema in routine care: results from a multicentre study in Germany. *Br J Dermatol*. 2011;165(4):845-51.
7. Blair HA, Scott LJ. Alitretinoin: A Review in Severe Chronic Hand Eczema. *Drugs*. 2016;76(13):1271-1279.
8. Ruzicka T, Lynde CW, Jemec GB, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol*. 2008;158(4):808-17.
9. Dirschka T, Reich K, Bissonnette R, Maares J, Brown T, Diepgen TL. An open-label study assessing the safety and efficacy of alitretinoin in patients with severe chronic hand eczema unresponsive to topical corticosteroids. *Clin Exp Dermatol*. 2011;36(2):149-54.
10. Lynde C, Cambazard F, Ruzicka T, Sebastian M, Brown TC, Maares J. Extended treatment with oral alitretinoin for patients with chronic hand eczema not fully responding to initial treatment. *Clin Exp Dermatol*. 2012;37(7):712-7.
11. Bissonnette R, Worm M, Gerlach B, et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *Br J Dermatol*. 2010;162(2):420-6.
12. Skudlik C, Weisshaar E, Scheidt R, et al. Multicenter study "Medical-Occupational Rehabilitation Procedure Skin--optimizing and quality assurance of inpatient-management (ROQ)". *J Dtsch Dermatol Ges*. 2009;7(2):122-6.
13. Skudlik C, Weisshaar E, Scheidt R, et al. First results from the multicentre study rehabilitation of occupational skin diseases--optimization and quality assurance of inpatient management (ROQ). *Contact Dermatitis*. 2012;66(3):140-7.
14. Skudlik C, Dulon M, Pohrt U, Appl KC, John SM, Nienhaus A. Osnabrueck hand eczema severity index--a study of the interobserver reliability of a scoring system assessing skin diseases of the hands. *Contact Dermatitis*. 2006;55(1):42-7.
15. Dulon M, Skudlik C, Nubling M, John SM, Nienhaus A. Validity and responsiveness of the Osnabruck Hand Eczema Severity Index (OHSI): a methodological study. *Br J Dermatol*. 2009;160(1):137-42.
16. Apfelbacher C, Molin S, Weisshaar E, et al. Characteristics and provision of care in patients with chronic hand eczema: updated data from the CARPE registry. *Acta Derm Venereol*. 2014;94(2):163-7.
17. Apfelbacher CJ, Ofenloch RF, Weisshaar E, et al. Chronic hand eczema in Germany: 5-year follow-up data from the CARPE registry. *Contact Dermatitis*. 2019;80(1):45-53.
18. Barati Sedeh F, Ebbelohj NE, Agner T, Caroe TK. Systemic therapy and the use of complementary and alternative medicine in patients with recognized occupational hand

- Accepted Article
- eczema in Denmark: A cross-sectional questionnaire-based study. *Contact Dermatitis*. 2020;82(5):272-278.
19. Brans R, Skudlik C, Weisshaar E, et al. Association between tobacco smoking and prognosis of occupational hand eczema: a prospective cohort study. *Br J Dermatol*. 2014;171(5):1108-15.
 20. Halioua B, Paul C, Berbis P, et al. Efficacy and safety of oral alitretinoin as treatment for chronic hand eczema in France: a real-life open-label study. *Eur J Dermatol*. 2019;29(1):59-66.
 21. Politiek K, Christoffers WA, Coenraads PJ, Schuttelaar MA. Alitretinoin and acitretin in severe chronic hand eczema; results from a retrospective daily practice study. *Dermatol Ther*. 2016;29(5):364-371.
 22. Diepgen TL, Pfarr E, Zimmermann T. Efficacy and tolerability of alitretinoin for chronic hand eczema under daily practice conditions: results of the TOCCATA open study comprising 680 patients. *Acta Derm Venereol*. 2012;92(3):251-5.
 23. Brans R, John SM. Clinical patterns and associated factors in patients with hand eczema of primarily occupational origin. *J Eur Acad Dermatol Venereol*. 2016;30(5):798-805.
 24. Cvetkovski RS, Rothman KJ, Olsen J, et al. Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. *Br J Dermatol*. 2005;152(1):93-8.
 25. Meding B. Epidemiology of hand eczema in an industrial city. *Acta Derm Venereol Suppl (Stockh)*. 1990;153:1-43.
 26. Hald M, Agner T, Blands J, et al. Clinical severity and prognosis of hand eczema. *Br J Dermatol*. 2009;160(6):1229-36.
 27. Veien NK, Hattel T, Laurberg G. Hand eczema: causes, course, and prognosis I. *Contact Dermatitis*. 2008;58(6):330-4.
 28. Veien NK, Hattel T, Laurberg G. Hand eczema: causes, course, and prognosis II. *Contact Dermatitis*. 2008;58(6):335-9.

Table 1: Age of patients who reported or negated treatment with alitretinoin prior to the tertiary individual prevention programme (TIP)

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

TIP = tertiary individual prevention programme

Table 2: Annual rate of patients who reported treatment with alitretinoin prior to the tertiary individual prevention programme (TIP)

	Total n/n _{total} (%)	men n/n _{total} (%)	women n/n _{total} (%)	<i>P</i> 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

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

	total n=348	men n=202 (58,0%)	women n=146 (42,0%)	P value
Age in years, mean $\pm$ SD	49.78 $\pm$ 10.24	49.43 $\pm$ 10.09	50.27 $\pm$ 10.45	.450
Tobacco smoker, n (%)	140 (40.2)	70 (34.7)	70 (47.9)	.013
Duration of skin disease before TIP in years, mean $\pm$ SD	N=313 8.93 $\pm$ 8.50	n= 183 9.31 $\pm$ 8.46	n= 130 8.39 $\pm$ 8.56	.350
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 $\pm$ SD	n=346 6.55 $\pm$ 3.18	n=201 6.15 $\pm$ 3.10	n=145 7.11 $\pm$ 3.21	.007
Systemic treatment other than alitretinoin in the past, n (%)	62 (17.8)	42 (20.8)	20 (13.7)	.088
Other systemic treatment in the past ^{††} , n/n _{total} (%)				
• 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

OHSI = Osnabrueck Hand Eczema Severity Index, SD = standard deviation, TIP = tertiary individual prevention programme

[†] based on OHSI

^{††} more than one possible

Table 4: Comparison of patients in which treatment with alitretinoin was initiated during the tertiary individual prevention programme (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 in years (total) mean $\pm$ SD (range)	52.16 $\pm$ 10.02 (21-65)	48.55 $\pm$ 11.35 (17-64)	.050
Age in years (women) mean $\pm$ SD (range)	55.07 $\pm$ 7.02 (37-65)	49.09 $\pm$ 11.64 (17-64)	.055
Age in years (men) mean $\pm$ SD (range)	50.70 $\pm$ 11.040 (21-65)	47.93 $\pm$ 11.03 (21-64)	.232
Tobacco smokers, n (%)	21 (46.7)	84 (40.4)	.438
Duration of skin disease prior to TIP in years, mean $\pm$ SD	n= 39 8.69 $\pm$ 8.82	n= 193 8.83 $\pm$ 9.24	.938
Hand eczema, n (%)	45 (100)	196 (94.2)	.133
Subtype of hand eczema, n (%)			
• 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 eczema [†] , n (%)	27 (60.0)	96 (49.0)	.092
OHSI at admission, mean $\pm$ SD	8.91 $\pm$ 3.47	7.43 $\pm$ 3.32	.014
OHSI at dismissal, mean $\pm$ SD	n = 42: 5.88 $\pm$ 2.48	n = 206: 4.20 $\pm$ 2.13	< .001
Systemic therapy prior to TIP, n (%)	11 (24.4)	47 (22.6)	.789
Type of systemic therapy prior to TIP ^{††} , n (%)			
• Alitretinoin	10 (22.2)	40 (19.2)	.648
• Acitretin	3 (6.7)	4 (1.9)	.109
• Cyclosporine	2 (4.4)	4 (1.9)	.290
• Methotrexate	0 (0)	2 (1.0)	1.000
• Fumaric acid	1 (2.2)	2 (1.0)	.446

OHSI = Osnabrueck Hand Eczema Severity Index, SD = standard deviation, TIP = tertiary individual prevention programme

[†] based on OHSI

^{††} more than one possible

Supplemental Table S1: Self-reported data related to treatment with alitretinoin prior to the tertiary individual prevention programme (TIP) in patients with hand eczema

	n (%) patients
Daily dose • 30 mg • 10 mg • 10 and 30 mg • 20 mg • unknown	n _{total} = 303 143 (47.2) 16 (5.3) 57 (18.8) 2 (0.7) 85 (28.1)
Number of months with at least one day of treatment, mean ± SD (range) ⁺	n _{total} = 274 6.40 ± 7.60 (1-63)
Treatment months with at least one day of treatment* • 1 month • 2-3 months • 4-6 months • 7-9 months • 10-12 months • > 12 months	n _{total} = 274 62 (22.6) 49 (17.9) 78 (28.5) 43 (15.7) 21 (7.7) 21 (7.7)
Number of treatment cycles • 1x • 2x • 3x • > 3x	n _{total} = 285 247 (86.6) 30 (10.5) 6 (2.1) 2 (0.7)
Adverse events	n _{total} = 303 142 (46.9)
Most common adverse events ⁺⁺ • headache • hyperlipidemia • gastrointestinal complaints • visual impairments/photophobia • depression • unclassified psychiatric disorder	n _{total} = 303 41 (13.5) 30 (9.9) 23 (7.6) 14 (4.6) 6 (2.0) 6 (2.0)
Course of disease • complete healing • improvement • no improvement • worsening • unknown	n _{total} = 303 24 (7.9) 74 (24.4) 103 (34.0) 2 (0.7) 100 (33.0)

⁺ only the longest treatment period in patients with more than one treatment cycle

⁺⁺ more than one possible

Supplemental Table S2: Comparison of patients with hand eczema reporting improvement or healing of the disease (n=98) with those reporting no improvement or worsening of the disease (n=105) during treatment with alitretinoin prior to the tertiary individual prevention programme (TIP)

	Positive response (improvement or healing)	No response (no improvement or worsening)	<i>P</i> value
Women, n/n _{total} (%)	38/79 (48.1)	41/79 (51.9)	.968
Men, n/n _{total} (%)	60/124 (48.4)	64/124 (51.6)	
Tobacco smokers, n/n _{total} (%)	32/77 (41.6)	45/77 (58.4)	.134
No tobacco smokers, n/n _{total} (%)	66/126 (52.4)	60/126 (47.6)	
Duration of disease in years, mean ± SD (range)	n=87 9.36 ± 9.01 (1-47)	n=92 10.12 ± 9.53 (1-44)	.583
Age in years, mean ± SD (range)	n=98 50.62 ± 10.12 (22-64)	n=105 48.34 ± 11.34 (20-68)	.133
OHSI at admittance, mean ± SD (range)	n=97 6.03 ± 3.14 (1-15)	n=105 7.03 ± 3.20 (1-14)	.027
ICD of hands, n/n _{total} (%)	48/98 (49.0)	50/98 (51.0)	.791
No ICD of hands, n/n _{total} (%)	49/105 (47.6)	55/105 (52.4)	
Atopic HE, n/n _{total} (%)	57/133 (42.9)	76/133 (57.1)	.033
No atopic HE, n/n _{total} (%)	41/70 (58.6)	29/70 (41.4)	
ACD of hands, n/n _{total} (%)	4/11 (36.4)	7/11 (63.6)	.416
No ACD of hands, n/n _{total} (%)	94/192 (49.0)	98/192 (51.0)	
Hyperkeratotic HE, n/n _{total} (%)	33/51 (64.7)	18/51 (35.3)	.007
No hyperkeratotic HE, n/n _{total} (%)	65/152 (42.8)	87/152 (57.2)	
Vesicular HE [†] , n/n _{total} (%)	34/85 (40.0)	51/85 (60.0)	.045
No vesicular HE [†] , n/n _{total} (%)	64/118 (54.2)	54/118 (45.8)	

ACD = allergic contact dermatitis, HE = hand eczema, ICD = irritant contact dermatitis, OHSI = Osnabrueck Hand Eczema Severity Index, SD = standard deviation,

[†] based on OHSI