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ORIGINAL RESEARCH ARTICLE

Drug Survival of Oral Retinoids in Hidradenitis Suppurativa: A Real-Life Cohort Study

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Abstract

Introduction Cohort studies on the use of retinoids for hidradenitis suppurativa (HS) have yielded contradicting results. As the clinical presentation of HS is heterogeneous, with different predilection sites and hallmark features, it can be hypothesized that HS phenotypes are associated with the effectiveness of specific retinoid treatments.

Objectives The aim of this study was to evaluate the drug survival of oral retinoids in the treatment of HS and to establish predictors for longer treatment duration.

Methods A retrospective, dual-center study was conducted in the Netherlands in adult HS patients treated with oral retinoids between 2011 and 2021. Drug survival analyses were performed through Kaplan-Meier survival curves. Additionally, Cox regression models were used to determine predictors for a longer drug survival.

Results In total, 102 patients were included. Overall drug survival of (low-dose) isotretinoin ($n = 66$) at 12 and 24 months was 44.2% and 15.5%, respectively. Termination of treatment was mostly due to ineffectiveness (26%). Presence of widespread comedones ($p = 0.03$) and the use of concomitant systemic medication ($p = 0.04$) were associated with a prolonged treatment duration. For acitretin ($n = 36$), the overall drug survival was 42.0% at 12 months and 37.4% at 24 months, and was also predominantly determined by ineffectiveness (28%). Interestingly, the scarring folliculitis phenotype ($p < 0.05$) was associated with prolonged drug survival time for acitretin treatment relative to the regular phenotype.

Conclusion Comparable drug survival rates at 12 months for isotretinoin and acitretin were found. HS patients with widespread comedones and the scarring folliculitis phenotype could benefit from treatment with isotretinoin or acitretin, respectively.

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Key Points

Retinoids are used for the treatment of hidradenitis suppurativa (HS); however, current literature shows discrepant reports of effectiveness.

Drug survival, defined as the probability of the continuation of drugs, contributes to information on their real-life performance.

Isotretinoin and acitretin showed a comparable treatment survival after 12 months, while after 24 months, acitretin was superior to (low-dose) isotretinoin.

1 Introduction

Hidradenitis suppurativa (HS) is a chronic, heterogeneous, auto-inflammatory skin disease causing (pseudo) comedones, inflammatory nodules, abscesses, and/or tunnels [1]. While long-term antibiotics, immunomodulatory drugs, and surgery are cornerstones in the treatment of HS, the role of systemic retinoids in HS treatment remains controversial [2, 3]. In the North American guidelines, both isotretinoin and acitretin are considered second- or third-line treatment options or are used in patients with severe concomitant acne, whereas only acitretin is suggested in the European guidelines for the management of HS [3–5]. Nonetheless, other systemic retinoids like isotretinoin remain widely used in daily practice based on the clinical experience of treating physicians and discrepant clinical study results. Both isotretinoin and acitretin might perform favorably when factoring in comorbidities (e.g. acne vulgaris) and their effect on certain HS phenotypes.

Various phenotype classifications have been proposed in HS [6–8]. In this manuscript, we utilize the phenotype classification refined by Dudink et al. that encompasses the following phenotypes: the frictional furunculoid, conglobata, scarring folliculitis, and regular types, each with their own predilection sites and hallmark lesions [9].

A possible explanation for the discordant results of different retinoids might lie in their different modes of action, potentially related to the different phenotypic presentations of HS. Isotretinoin mainly affects sebocytes and could therefore reduce the amount of comedones, whereas acitretin alters the keratinocyte proliferation, reducing possible infundibular hyperkeratosis, follicular occlusion, and subsequently epidermal cysts [10–12]. When taking the different features and possible diverse etiopathogenesis of the aforementioned phenotypes into account, it can be hypothesized that an inter-phenotype difference in response to retinoid treatment exists [13–15]. Therefore, we investigated the drug survival (defined as the time a patient remains on a specific therapy) of isotretinoin and acitretin to measure drug effectiveness in real-life as drug survival studies are regarded as a proxy for effectiveness in clinical practice. Additionally, we analyzed possible predictors for prolonged drug survival in HS patients.

2 Methods

2.1 Design

A dual-center, retrospective, cohort study was performed at the departments of Dermatology of the University Medical Center Groningen (UMCG) and the Erasmus University Medical Center Rotterdam (EMC) in the Netherlands. Inclusion criteria were patients ≥ 18 years with a physician-verified diagnosis of HS and treatment with oral retinoids for HS between 2011 and June 2021. Patients with Down's syndrome ($n = 4$) or patients who were treated with retinoids for a different indication ($n = 10$) were excluded. Because of the retrospective nature of this study, exemption from reviewing was granted by the medical ethical board from the UMCG.

2.2 Patient Characteristics

The patient data were extracted from electronic patient files: sex, age at onset of HS symptoms, age at start of retinoid treatment, body mass index (BMI) at start of treatment, smoking status at start of treatment, comorbidities, previous or active acne vulgaris or pilonidal cyst, family history of HS, presence of widespread comedones, phenotype, and the treating center. Phenotypes were categorized as previously published, and stratified accordingly to the regular type, frictional furuncle type, scarring folliculitis type, and conglobata type [9, 15]. Both phenotype and presence of widespread comedones were assessed based on photographic images by three physicians trained in the field of HS (KB, PA, KD) who were blinded to treatment. In the event of discrepancies, the patient in question was discussed among the physicians and a consensus was formed. If no sufficient photographic material was present to reach a conclusion, as was the case in a handful of patients, the phenotype and presence of widespread comedones were extracted from the patient charts. Disease severity was assessed using the International Hidradenitis Suppurativa Severity Score System (IHS4), and the (refined) Hurley score based on patient charts [16–18].

2.3 Treatment Characteristics

Type of therapy (acitretin or isotretinoin), treatment regimens, start and stop dates, reason for discontinuation, previous treatment with retinoids, concomitant medication (topical or systemic), and side effects were listed. Surgical procedures for HS during treatment were recorded and included deroofing, skin-tissue sparing excision with electrosurgical peeling (STEEP), and limited or wide excision surgery.

2.4 Statistical Analysis

2.4.1 Descriptive Statistics

Normality was assessed using the Kolmogorov-Smirnov test, showing all data to be non-normally distributed. Continuous variables were presented as median and interquartile range (IQR). Categorical data were reported as the number

of patients and percentage (*n*, %). Mann–Whitney *U* tests were used to analyze continuous data. For categorical variables, the Chi-squared test was used.

2.4.2 Multiple Imputations

Multiple imputation (MI) treats the observed varying percentage of missingness across participants, using the mice package version 3.13.0 on R version 1.4.1103. The data set was tested for the assumption of missing completely at random (MCAR; Little's MCAR test $p = 0.34 > 0.05$). BMI, smoking status, ethnicity, (refined) Hurley stage, IHS4 categories, family history, disease duration, and age of onset were imputed through fully conditionally specified models. The continuous IHS4 was deemed not suitable for imputation and was removed from the analysis. Random Forest (for categorical diagnostic outcomes) and Classification and Regression Tree (the rest of the variables for imputation) methods were used to construct the imputation model. The analytical results were pooled based on the Rubin's rules using in-house developed script (Naderi, et al. under review). For details on the imputed data see Supplementary Methods (appendix S1 in the electronic supplementary material [ESM]).

2.4.3 Drug Survival Analyses

Per retinoid, the general drug survival was analyzed using Kaplan–Meier survival curves and compared using Cox regression analyses. Separate drug survival curves were generated for discontinuation due to ineffectiveness, side effects, and remission. In the analyses, patients were censored at the date of their last visit, when lost to follow-up, or when the retinoid was stopped for reasons other than ineffectiveness, side effects, or remission. If a patient discontinued treatment due to a combination of ineffectiveness and side effects, it was taken into account as having an event in the general drug survival analyses, ineffectiveness analyses, and side effect analyses. Moreover, selected baseline variables were assessed as possible predictors for longer drug survival time in univariate Cox regression analysis: sex, age, BMI, treating center, disease duration, smoking status, previous retinoid use, widespread comedones, previous or active pilonidal cysts, previous or active acne vulgaris, categorical IHS4, (refined) Hurley stage, concomitant comedication, surgery during treatment, and phenotype. To assess the effect of concomitant immunosuppressive medication and surgery during treatment on the identification of possible predictors for longer drug survival, post-hoc Cox regression sub-analyses were performed excluding patients with concomitant immunosuppressive medication and surgery during treatment. Although classically Cox regression analyses define hazard ratio (HR) as a risk estimate per unit time to reach the outcome, here we used it to identify predictors for a longer treatment survival. Assumptions of the Cox regression analyses were tested using the time-dependent explanatory variables; if a $p < 0.05$ was found, the assumptions were not met and left out of the analyses. In the statistical analyses, differences with two-sided p values < 0.05 were regarded as statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY; USA).

3 Results

3.1 Patient Characteristics

In total, 102 treatment series with an oral retinoid were identified in 98 HS patients, of whom 66 patients (65%) were treated with (low-dose) isotretinoin and 36 (35%) with acitretin. In both groups, the majority was male (61%), most were current or ex-smokers (92%), and widespread comedones were seen in 52% of the patients (Table 1). According to the IHS4 score, 48% of the patients were categorized as having mild disease, 31% as moderate, and 21% as severe at the start of treatment. The most frequent phenotypes were the regular type (38%) and the conglobata type (34%). Previous or active acne vulgaris was present in 28% of the patients, and acne conglobata in 47%. Pilonidal cysts were seen in 13% of the cases, and dissecting cellulitis in 4%.

3.2 Treatment Characteristics

Overall median treatment duration was 7.0 months (IQR 3.0–13.0), see Table 2. The most commonly used dosages in both groups were 20–30 mg/day (70%). Concomitant systemic antibiotics (i.a., clindamycin/rifampicin, co-trimoxazole, and azithromycin) were administered to 21% of the patients, and 13% used other systemic treatment (e.g., biologics or prednisone). Most patients stopped treatment due to primary ineffectiveness (17%) or side effects (17%), while only three (3%) patients stopped because of remission. Loss to follow-up resulted in 26 patients (26%) being censored in the drug survival analyses. Side effects were recorded in 77 patients (76%), and most frequently consisted of mucosal dryness, headache, and nausea.

3.3 Isotretinoin

3.3.1 Drug Survival

Median overall drug survival for (low-dose) isotretinoin ($n = 66$) was 8.0 months (IQR 4.0–13.0), with an overall drug survival at 12 and 24 months of 44.2 and 15.5%,

Table 1 Patient characteristics

Characteristics	Total $N = 102$	Isotretinoin $n = 66$	Acitretin $n = 36$	p value*
Female sex, *n* (%)	40 (39)	31 (47)	9 (25)	**0.030**
Age of onset, median [IQR]	18.3 [14.3–23.3]	18.0 [14.0–22.0]	20.4 [15.7–24.8]	0.132
BMI, median [IQR]	26.5 [23.8–32.1]	25.9 [22.6–30.0]	28.3 [25.8–34.4]	**0.004**
Disease duration (years), median [IQR]	15.3 [8.8–24.7]	14.1 [7.2–20.0]	19.7 [10.3–31.5]	**0.015**
Age at start of treatment, median [IQR]	35.5 [29.0–45.0]	32.5 [25.8–40.3]	43.5 [33.0–51.8]	**0.001**
Positive family history, *n* (%)	41 (40)	28 (42)	13 (37)	0.651
Smoking status				
Current or ex-smoker, *n* (%)	94 (92)	60 (90)	34 (94)	0.494
Treating center				
EMC, *n* (%)	47 (46)	39 (59)	8 (22)	< **0.001**
UMCG, *n* (%)	55 (54)	27 (41)	28 (78)	
Hurley classification at baseline				
Stage I, *n* (%)	67 (66)	45 (69)	22 (61)	0.501
Stage II, *n* (%)	30 (29)	19 (28)	11 (31)	
Stage III, *n* (%)	5 (5)	2 (4)	3 (8)	
Refined Hurley at baseline				
Mild (IA, IIA), *n* (%)	33 (32)	25 (37)	8 (22)	0.228
Moderate (IB, IIB), *n* (%)	18 (18)	12 (18)	6 (17)	
Severe (IC, IIC, III), *n* (%)	51 (50)	29 (45)	22 (61)	
IHS4 at baseline				
Mild (≤ 3), *n* (%)	49 (48)	31 (48)	18 (50)	0.361
Moderate (4–10), *n* (%)	32 (31)	23 (35)	9 (25)	
Severe (≥ 11), *n* (%)	21 (21)	12 (18)	9 (25)	
Phenotype				
Regular type, *n* (%)	38 (37)	31 (47)	7 (19)	**0.020**
Frictional furuncle type, *n* (%)	9 (9)	4 (6)	5 (14)	
Scarring folliculitis type, *n* (%)	20 (20)	9 (14)	11 (31)	
Conglobata type, *n* (%)	35 (34)	22 (33)	13 (36)	
Widespread comedones, *n* (%)	53 (52)	30 (46)	23 (64)	0.075
Comorbidities				
None, *n* (%)	13 (13)	6 (9)	7 (19)	0.134
Acne vulgaris/tarda, *n* (%)	29 (28)	22 (33)	7 (19)	
Acne conglobata, *n* (%)	48 (47)	33 (50)	15 (42)	
Dissecting cellulitis scalp, *n* (%)	4 (4)	4 (6)	0	
Metabolic disorders, *n* (%)	16 (16)	6 (9)	10 (28)	
Psychiatric disorders, *n* (%)	17 (17)	8 (12)	9 (25)	
Pilonidal cyst, *n* (%)	13 (13)	6 (9)	7 (19)	
Other skin disorders, *n* (%)	20 (20)	14 (21)	6 (17)	
Other, *n* (%)	44 (43)	27 (41)	17 (47)	

*Mann Whitney *U* tests were used to analyze continuous variables to determine the difference between isotretinoin and acitretin, as none of the data was normally distributed. For categorical variables, Chi-squared tests were used. Normality was assessed using the Kolmogorov-Smirnov test. *P* values of 0.05 or lower are regarded as significant and shown in bold text

BMI body mass index, *HS* hidradenitis suppurativa, *IHS4* International Hidradenitis Suppurativa Severity Score System, *IQR* interquartile range, *EMC* Erasmus Medical Center, *UMCG* University Medical Center Groningen

respectively (Fig. 1A). For discontinuation due to primary and secondary ineffectiveness ($n = 17$), the 12 and 24 months' drug survival was 75.8 and 48.1%, respectively (Fig. 1B). For side effects ($n = 12$), this was 81.2 and 52.4% (Fig. 1C); and for remission ($n = 2$), both were 92.6% (Fig. 1D).

Table 2 Treatment characteristics

Characteristics	Total $N = 102$	Isotretinoin $n = 66$	Acitretin $n = 36$	p value*
Dosage				
< 20 mg/day, *n* (%)	13 (13)	7 (11)	6 (17)	**0.016**
20–30mg/day *n* (%)	71 (70)	48 (73)	23 (64)	
> 30 mg/day, *n* (%)	18 (18)	11 (17)	7 (19)	
Change in dosage (yes), *n* (%)	28 (28)	17 (26)	11 (31)	0.604
Previous retinoid use, *n* (%)	43 (42)	28 (42)	15 (42)	0.914
Treatment duration (months), median [IQR]	7.0 [3.0–13.0]	7.5 [3.8–13.0]	6.0 [3.0–18.0]	0.548
Supplementary treatment				
None, *n* (%)	65 (64)	39 (59)	26 (72)	0.204
Topical, *n* (%)	3 (3)	3 (5)	0	
Systemic antibiotics, *n* (%)	21 (21)	13 (20)	8 (22)	
Other systemic treatment, *n* (%)	13 (13)	11 (17)	2 (6)	
Side effects				
Yes, *n* (%)	77 (76)	51 (77)	26 (72)	**0.027**
No, *n* (%)	13 (13)	5 (8)	8 (22)	
Unkown, *n* (%)	6 (6)	6 (9)	0	
Missing, *n*	6	4	2	
Surgery during treatment (yes), *n* (%)	24 (24)	15 (23)	9 (25)	0.796
Treatment ongoing (yes), *n* (%)	16 (16)	10 (15)	6 (17)	0.841
Stop reason				
Primary ineffectiveness, *n* (%)	17 (17)	9 (14)	8 (22)	0.888
Secondary ineffectiveness, *n* (%)	8 (8)	6 (9)	2 (6)	
Side effects, *n* (%)	17 (17)	10 (15)	7 (19)	
Primary ineffectiveness and side effects, *n* (%)	1 (1)	1 (2)	0	
Secondary ineffectiveness and side effects, *n* (%)	1 (1)	1 (2)	0	
Loss to follow-up, *n* (%)	26 (26)	17 (26)	9 (25)	
Remission, *n* (%)	3 (3)	2 (3)	1 (3)	
Other, *n* (%)	13 (13)	10 (15)	3 (8)	

*Mann Whitney *U* tests were used to analyze treatment duration between the isotretinoin and acitretin group. For categorical variables, Chi-squared tests were used. *P* values of 0.05 or lower are regarded as significant and shown in bold text

IQR interquartile range

3.3.2 Reasons for Discontinuation

Out of the 66 patients who received isotretinoin, 49 (74%) discontinued treatment. Seventeen (26%) patients were lost to follow-up, nine (14%) stopped due to primary ineffectiveness, another six (9%) due to secondary ineffectiveness, and ten (15%) due to side effects. Moreover, ten patients (15%) stopped for other reasons; one because of enrollment in a clinical trial (1.5%), one due to a COVID-19 infection (1.5%), one as a result of a pregnancy wish (1.5%), and the remaining seven for unknown reasons (10.6%). Only two (3%) patients stopped treatment because of remission of disease, of which one used adjuvant prednisone (20 mg) for 3 months. No patient discontinued treatment due to abnormal laboratory findings.

3.3.3 Cox Regression Analysis

Out of the tested variables, only the presence of widespread comedones and the use of comedication were significantly associated with a longer drug survival time with an HR of 0.46 (95% CI 0.23–0.92; $p = 0.03$) and 0.50 (95% CI 0.25–0.98; $p = 0.04$), respectively, see Table 3.

3.3.4 Post-hoc Cox Regression Analysis

Twenty-two HS patients with concomitant immunosuppressive medication and/or surgery during treatment were excluded for the post-hoc analysis. No new predictors for extended drug survival were identified, while the presence of widespread comedones remained significantly associated

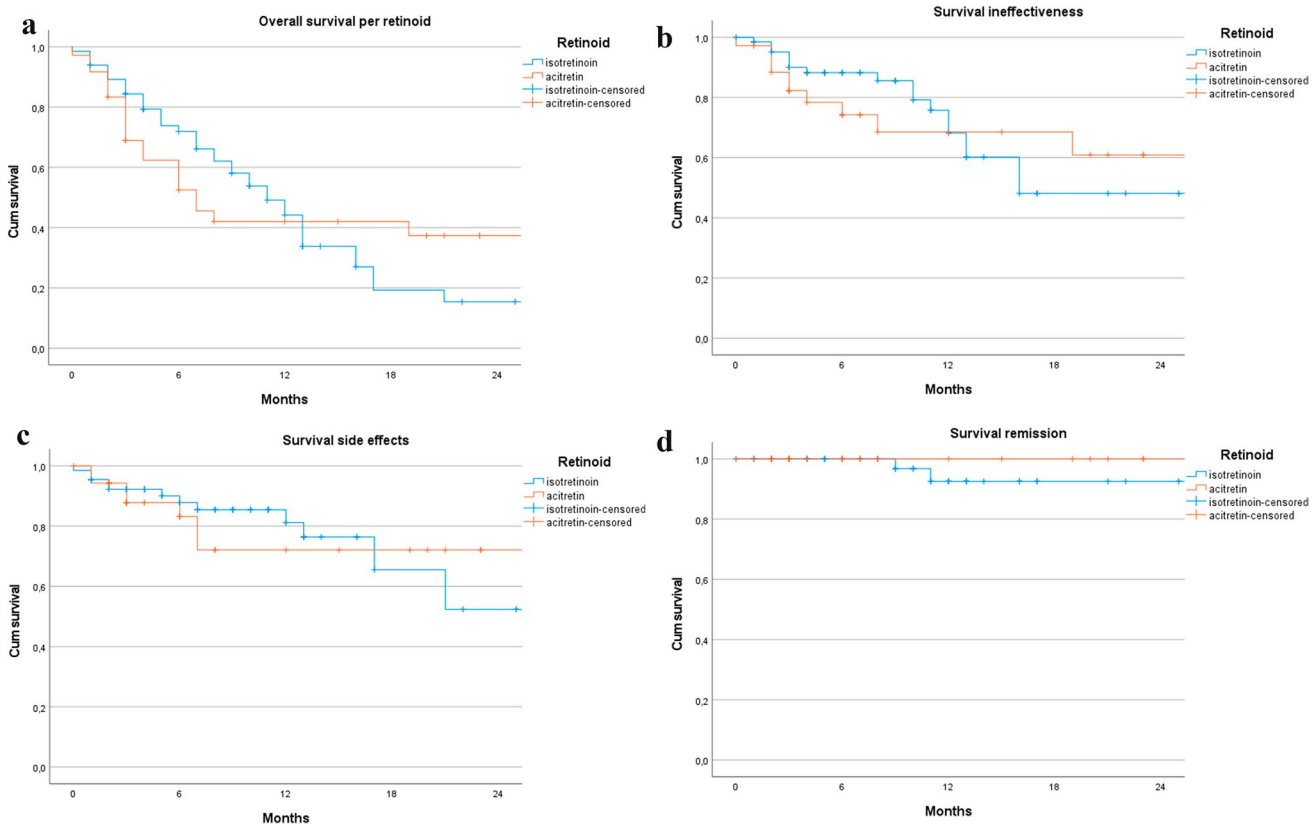

Fig. 1 Kaplan–Meier survival curves with the cumulative survival per retinoid; **A** overall survival, **B** split for ineffectiveness, **C** split for side effects, **D** split for remission

with a prolonged drug survival with an HR of 0.45 (95% CI 0.21–0.99; $p < 0.05$), see Supplementary Table 1 in the ESM.

3.4 Acitretin

3.4.1 Drug Survival

A median overall drug survival of 6.0 months (IQR 3.0–18.0) was found for acitretin. The overall drug survival ($n = 21$) at 12 and 24 months was 42.0% and 37.4%, respectively (Fig. 1A). For discontinuation due to primary and secondary ineffectiveness ($n = 10$), the drug survival was 68.5% and 60.9% (Fig. 1B), while the drug survival related to side effects ($n = 7$) were both 72.1% (Fig. 1C). For remission ($n = 1$), the 12- and 24-month survival was 100% for both time points, meaning no patient stopped because of remission during this timeframe (Fig. 1D).

3.4.2 Reasons for Discontinuation

In total, 28 patients (76%) discontinued treatment with acitretin. Nine patients (24%) were lost to follow-up, eight patients (22%) stopped due to primary ineffectiveness, two (6%) patients due to secondary ineffectiveness, and seven patients (19%) due to side effects. Only one (3%) patient stopped treatment because of remission of disease after 35 months. Another three (8%) patients stopped for other reasons; one (3%) as a result of a possible allergic skin reaction, one (3%) as a result of an elevated γ-glutamyl transferase (GGT) level related to acitretin, and one (3%) for unknown reasons. For an illustrative photographic example of an HS patient during treatment with acitretin, see Fig. 2.

3.4.3 Cox Regression Analysis

Out of the tested variables, only the scarring folliculitis phenotype was significantly associated with a prolonged treatment survival (HR 0.27, 95% CI 0.08–0.98; $p < 0.05$) compared with the regular phenotype (Table 3).

3.4.4 Post-hoc Cox Regression Analysis

Ten HS patients with concomitant immunosuppressive medication and/or surgery during treatment were excluded for the post-hoc analysis (Supplementary Table 1, see ESM). While the scarring folliculitis phenotype was no longer significantly associated with a prolonged drug survival time,

Table 3 Univariate Cox regression analysis per retinoid

	Total $N = 102$		Isotretinoin $n = 66$		Acitretin $n = 36$	
	HR (95% CI)	p value*	HR (95% CI)	p value*	HR (95% CI)	p value*
Female sex	1.25 [0.75–2.08]	0.40	1.26 [0.67–2.38]	0.48	1.40 [0.54–3.63]	0.48
Age	0.98 [0.96–1.00]	0.11	0.97 [0.94–1.01]	0.10	0.99 [0.96–1.03]	0.55
BMI	0.96 [0.96–0.97]	0.19	0.96 [0.96–0.96]	0.25	0.95 [0.95–0.96]	0.33
Center[b]	0.67 [0.40–1.13]	0.13	0.68 [0.36–1.29]	0.24	0.54 [0.16–1.82]	0.32
Disease duration	0.99 [0.99–0.99]	0.28	0.98 [0.98–0.98]	0.21	1.00 [1.00–1.00]	0.90
Current or ex-smoker	1.43 [0.85–2.41]	0.48	1.75 [0.87–3.54]	0.35	1.27 [0.16–10.11]	0.81
Retinoid naïve	1.04 [0.62–1.73]	0.88	1.32 [0.70–2.48]	0.39	0.82 [0.34–1.96]	0.65
Widespread comedones		[a]	**0.46 [0.23–0.92]**	**0.03**	0.44 [0.16–1.03]	0.06
Pilonidal cyst	0.81 [0.39–1.68]	0.57	0.74 [0.26–2.08]	0.56	1.00 [0.35–2.84]	1.00
Acne vulgaris	1.58 [0.92–2.71]	0.10	1.35 [0.71–2.58]	0.36	2.17 [0.78–6.10]	0.14
Hurley classification						
Stage I	*Reference*		*Reference*		*Reference*	
Stage II	1.00 [0.85–1.18]	0.99	0.97 (0.75–1.25)	0.93	0.98 [0.61–1.59]	0.97
Stage III	0.79 [0.30–2.12]	0.75		NP	1.15 [0.36–3.61]	0.86
Refined Hurley classification						
Mild (IA, IIA)	*Reference*		*Reference*		*Reference*	
Moderate (IB, IIB)	0.82 [0.60–1.12]	0.61	0.55 [0.34–0.87]	0.21	1.44 [0.44–4.73]	0.64
Severe (IC, IIC, III)	1.01 [0.86–1.19]	0.97	0.85 [0.66–1.01]	0.65	1.27 [0.66–2.42]	0.68
ISH4 categories						
Mild	*Reference*		*Reference*		*Reference*	
Moderate	0.97 [0.79–1.19]	0.93	0.95 [0.70–1.29]	0.89	0.57 [0.13–2.58]	0.52
Severe	1.00 [0.69–1.47]	0.99	0.72 [0.34–1.56]	0.60	1.12 [0.57–2.21]	0.85
Comedication	**0.49 [0.28–0.86]**	**0.01**	**0.50 [0.25–0.98]**	**0.04**	0.41 [0.14–1.24]	0.12
Surgery		[a]		[a]	0.82 [0.32–2.13]	0.68
Phenotypes						
Regular	*Reference*	[a]	*Reference*		*Reference*	
Frictional furuncle			1.33 [0.39–4.50]	0.65	0.84 [0.21–3.37]	0.80
Scarring folliculitis			0.83 [0.31–2.24]	0.72	**0.27 [0.08–0.98]**	**< 0.05**
Conglobata			0.69 [0.33–1.44]	0.32	0.55 [0.19–1.61]	0.28

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *IHS4* International Hidradenitis Suppurativa Severity Score System, *NP* no p value, *UMCG* University Medical Center Groningen

*p value estimated from t-distribution of pooled HR Rubin's rules. P values of 0.05 or lower are regarded as significant and shown in bold text

[a]Assumptions were not met

[b]UMCG as reference

acne vulgaris was found to be associated with a longer drug survival time with an HR of 7.49 (95% CI 2.02–27.85; $p < 0.01$).

4 Discussion

This study evaluated the drug survival of (low-dose) isotretinoin and acitretin regimens in HS patients in a daily practice setting. Comparable modest 12-month treatment survival rates were found (44.2% for isotretinoin vs 42.0% for acitretin), with a favorable drug survival rate for acitretin after 24 months (15.5% for isotretinoin vs 37.4% for acitretin). In addition, we identified the presence of widespread comedones and concomitant medication for isotretinoin, and the scarring folliculitis phenotype for acitretin, as predictors for a longer drug survival. Furthermore, ineffectiveness and side effects were the predominant reasons to discontinue the treatment of both isotretinoin and acitretin.

The superior survival rate of acitretin relative to (low-dose) isotretinoin after 24 months might be explained by the different modes of action of these retinoids. Whereas isotretinoin mainly exerts its function by modulation of the sebaceous glands [19], acitretin directly modulates hyperkeratosis. The latter is deemed a primary pathogenic event

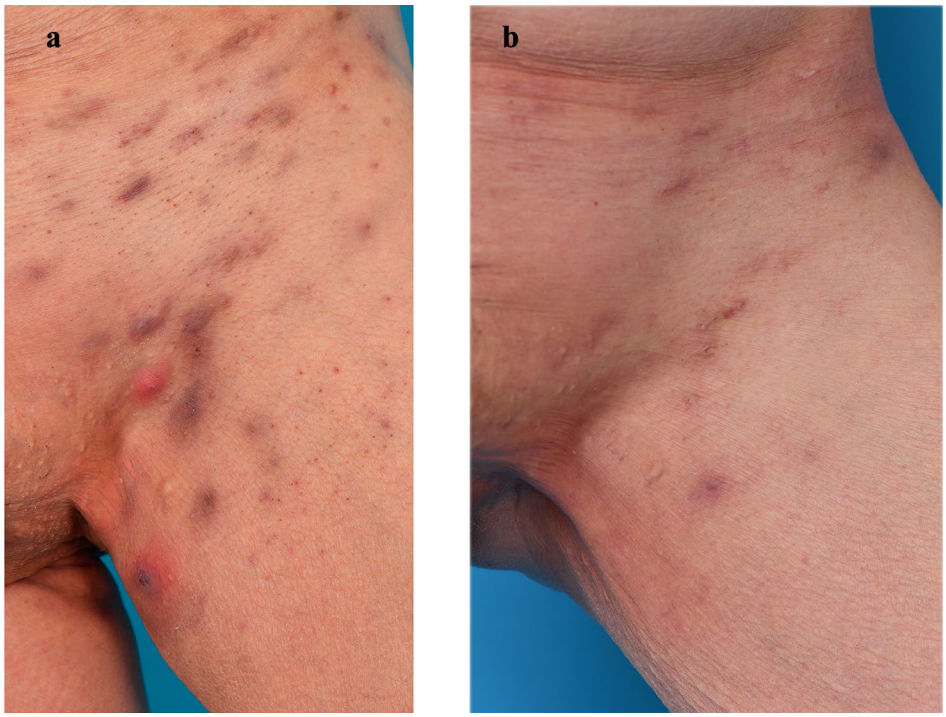

Fig. 2 Illustrative photographs of a hidradenitis suppurativa patient on long-term treatment with acitretin. On the left **A** a photograph at the start of treatment and on the right **B** a photograph after 28 months of treatment

in HS while involvement of the sebaceous glands has been shown to be secondary to established inflammation [1]. Therefore, acitretin could be expected to demonstrate a higher effectiveness and a longer drug survival than isotretinoin. Similarly, even though no prior drug survival studies exist regarding the use of retinoids in HS, the current clinical literature favors acitretin as a more effective treatment for HS than isotretinoin [3]. One case series ($n = 12$) consisting of severe, recalcitrant HS cases even reported remission in all patients treated with acitretin, while other studies examining isotretinoin in HS showed varying partial responses in16.1–64% of patients [20–23]. These clinical results of acitretin and isotretinoin coincided with our findings.

Ineffectiveness and side effects were the predominant reasons to discontinue the treatment of both retinoids. A prospective series of 17 patients investigating the efficacy of acitretin found the same determinants of treatment termination, with a reported drop-out rate of 47% of HS patients after 9 months of therapy [24]. In our study, we were not able to conclusively demonstrate the effectiveness of oral retinoids, due to a relatively high prevalence of discontinuation related to ineffectiveness and side effects ($n = 44$). However, clinical experience and other studies support the use of systemic retinoid therapy in at least a subgroup of HS patients [2, 3]. Additionally, other studies report greater success for at least isotretinoin in less severe cases, with better response for Hurley I and II versus Hurley III [21]. Even though our study included a high percentage of severe cases, no significant differences for drug survival could be demonstrated through Cox regression analyses.

Several predictors for a longer drug survival were identified in this study. For (low-dose) isotretinoin, the presence of widespread comedones and the use of concomitant medication proved to be indicative for longer drug survival, whereas for acitretin, the scarring folliculitis phenotype was found as a predictor for longer treatment duration. Interestingly, previous studies found that a history of pilonidal cysts, acne, and female gender were significantly associated with a beneficial response to isotretinoin treatment [21, 23, 25]. In contrast, our study identified a trend in which treatment with retinoids was terminated earlier in HS patients with comorbid acne vulgaris. As retinoid therapy is also a mainstay in acne treatment, it could be hypothesized that with the resolution of patients' acne, discontinuation of therapy ensued, skewing our drug survival data.

Another surprising finding which is discrepant with existing literature was the overabundance of isotretinoin-treated patients in our cohort relative to those treated with acitretin. Most HS guidelines recommend acitretin and classify isotretinoin as unsuited for HS therapy, mainly due to its demonstrated lack of efficacy [3, 4]. Several reasons for this could exist. First, a high population of comorbidities, such as acne vulgaris and acne conglobata, were present in our population; both diseases are treated frequently with isotretinoin. Moreover, although all retinoids are known teratogens, acitretin has longer lasting teratogenic effects, making it even less suited

for treatment of female patients of reproductive age. The teratogenicity might also account for the paradoxical male dominance in this population, whereas in the regular HS population, females vastly outnumber males [2, 12, 26].

As to be expected in a real-life cohort, the use of concomitant medication and surgery was highly prevalent in our study. Both are known effect modifiers for treatment effectiveness in HS, as was shown in another drug survival study in HS assessing adalimumab and infliximab [27]. For that reason, post-hoc analyses were performed, excluding patients with concomitant immunosuppressive medication and surgery. For treatment with isotretinoin, the presence of widespread comedones remained a predictor, as for treatment with acitretin, previous or active acne vulgaris became a predictor for shorter treatment survival and the scarring folliculitis subtype proved no longer a significant predictor for longer treatment survival. However, because of the relatively modest occurrence of concomitant acne vulgaris and scarring folliculitis, this finding might be attributable to statistical effects rather than a clinically relevant difference.

One of the study limitations was its retrospective design and use of hospital routine observations, leading to a notable number of patients lost to follow-up and thus a large proportion of missing data. To address these issues, multiple imputation was applied to address the issue of missing data, resulting in high-quality imputed data. Secondly, treatment compliance could not be controlled or measured. Furthermore, the fact that mainly low-dose isotretinoin regimens were used could have impacted our findings as well, as conclusions regarding isotretinoin effectiveness cannot be applied to full-dose therapy. Lastly, racial demographics (data not shown) yielded a study population of 15% of patients not being Caucasian, which is comparable to the general population of the Netherlands, but is most likely not representative of the global population [28, 29]. A systematic prospective study using routine real-world data or a randomized controlled trial could be a next step to confirm our findings and conclusions.

5 Conclusion

Isotretinoin and acitretin demonstrated comparable treatment survival after 12 months, while after 24 months, acitretin was superior to isotretinoin. Predictors for a longer drug survival are the presence of widespread comedones and concomitant medication for isotretinoin, and the scarring folliculitis phenotype for acitretin.

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Declarations

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Conflict of interest KB, PA, JH, BA, LP, AV, and KvS report no conflicts of interest. HvdZ has been an advisory board member for AbbVie, InflaRX, Novartis and a speaker for Galderma. BH reports fees from Janssen-Cilag (Advisory Boards, Educational grants, Consultations, Investigator Initiative Studies), AbbVie (Advisory Boards, Educational grants, Consultations, Investigator Initiative Studies), Novartis Pharma (Advisory Boards, Consultations, Investigator Initiative Studies), UCB Pharma (Advisory Boards, Consultations), Leo Pharma (Consultations), Solenne B.V. (Investigator Initiative Studies), Celgene (Consultations, Investigator Initiative Studies), Akari therapeutics (Consultations, Investigator Initiative Studies), Philips (Consultation), Roche (Consultation), Regeneron (Consultation) and Sanofi (Consultation), which fees were paid to the institution.

Research ethics The ethical committee of the University Medical Center Groningen UMCG verified that the Medical Research Involving Human Subjects Act (WMO) did not apply to this research.

Consent to participate/publish The authors affirm that human research participants provided informed consent for publication of the images in Fig. 2A, B.

Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KB, PA and KD. The first draft of the manuscript was written by KB and PA and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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