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CONCISE COMMUNICATION

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Anti-IL17 Secukinumab in hidradenitis suppurativa: A long-term drug survival analysis

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Abstract

Real-world data on the long-term effectiveness of the anti-IL17 agent secukinumab in treating moderate-to-severe Hidradenitis suppurativa (HS) are lacking. In this study, 24 patients with moderate–severe HS received five weekly subcutaneous injections followed by maintenance doses every 4 weeks. Primary outcomes included HiSCR, IHS4 reduction, and DLQI measures assessed at 12-week intervals. The median secukinumab drug survival was 16.0 months (range 3–51), with a 56.5% maximal response rate at 6 months and dropout exceeding 40% at 1 year. Baseline disease burden emerged as a key predictor of treatment response, overshadowing factors like sex or BMI. Prior systemic steroid use negatively impacts drug survival. The study underscores the critical 6-month window for assessing treatment efficacy, emphasizing the importance of initial induction dosing. Additionally, the newly developed scoring system, IHS4-55, showed analogies to the older HiSCR score in capturing treatment response. In this real-life scenario, challenges persist in HS management, necessitating innovative therapeutic approaches and predictive markers.

KEYWORDS
drug survival, hidradenitis suppurativa, IHS4, IL17, secukinumab

1 | BACKGROUND

Hidradenitis suppurativa (HS) is a chronic inflammatory condition affecting the hair follicles, characterized by a complex autoinflammatory pathogenesis.[1,2] Adalimumab, an anti-tumour necrosis factor (TNF)-alpha agent, has been the primary biologic therapy indicated for moderate to severe HS since 2015.[3] More recently, there has been an exploration of other biologic agents targeting different interleukins, such as the IL-17 axis.[4,5] The SUNSHINE and SUNRISE trials demonstrated the promising efficacy of the anti-IL-17 agent secukinumab in improving skin lesions associated with moderate-to-severe HS, leading to its recent approval in Europe.[5] Clinical responses, measured by the Hidradenitis Suppurativa Clinical Response (HiSCR) at 16 weeks—the primary endpoint for both trials—were achieved in 45%–46% of cases.[5] Importantly, the HiSCR endpoint was met in the secukinumab every 2 weeks group in both trials, while in the every 4 weeks group only in the SUNRISE. The clinical efficacy observed at week 16 was sustained to week 52, following either dose regimen of secukinumab. Despite these promising results, there is currently insufficient data regarding the sustained effectiveness of the treatment in real-world settings, particularly beyond the one-year mark. Additionally, there has been an oversight in identifying reliable indicators for cutaneous response. Recent reports have suggested specific factors, such as female gender and lower body mass index, as potential predictors for achieving HiSCR, although the level of evidence remains limited.[6–8]

Gabriele Roccuzzo and Federica Repetto Shared first authorship.

1.1 | Questions addressed

This study aims to evaluate the real-life effectiveness and drug survival of secukinumab in a cohort of patients with moderate to severe HS. It also seeks to investigate any associated clinical characteristics that may influence treatment response and long-term maintenance.

1.2 | Experimental design

Inclusion criteria comprised individuals aged ≥18 years with Hurley grade ≥2, comprehensive medical records, and a switch to anti-IL-17 secukinumab agent due to primary or secondary failure and/or unacceptable side effects with adalimumab. Each participant underwent a treatment regimen consisting of five weekly subcutaneous injections of 300 mg secukinumab, followed by a maintenance phase of 300 mg subcutaneously every 4 weeks. Ultrasound assessment was conducted when uncertainty arose in evaluating subclinical lesions. Clinical evaluations occurred every 12 weeks, with the following primary outcomes assessed at each evaluation: (1) achievement of clinical response HiSCR, (2) reduction in disease severity measured by IHS4 (International HS Severity Score System) (3) attainment of the new IHS4-55 score (defined as a reduction of at least 55% in the IHS4 score).[9,10] The impact of secukinumab on the patient's quality of life was assessed according to Dermatology Life Quality Index (DLQI) measures, recorded at each follow up evaluation.[11] Statistical analyses employed Mann–Whitney, Fisher's, and $\chi 2$ tests for continuous and paired nominal data. Drug survival was defined as the proportion of patients on treatment at a given time as per contemporary practices.[12] The metric was assessed using Kaplan–Meier curves alongside log-rank tests for statistical analysis. Cox regression and logistic regression analyses were used to explore potential clinical predictors of drug survival and clinical response. Model fitness was evaluated according to McFadden's formula and Hosmer & Lemeshow test. Collinearity diagnostics through Variance inflation factor (VIF) were used to rule out multicollinearity among independent variables. Odds Ratios (OR) with 95% confidence intervals (CI) were computed to display the strength of association between the potential predictors and the outcomes in study. This study was approved by the Ethical committee of 'AOU Città della Salute e della Scienza di Torino' (protocol number 0072203) and was conducted in accordance with the principles of the declaration of Helsinki.

2 | RESULTS

Table 1 provides a summary of the patients' characteristics. Among the 24 participants, there was a slight female prevalence (62.5%), with a mean age of 38 (*sd* 15.0) and a mean BMI of 27.2 (*sd* 4.9). Notably, 18 out of 24 patients (75%) were active smokers. At the onset of secukinumab therapy, 13 patients (54.2%) were classified as Hurley 2, and 11 (45.8%) as Hurley 3. In terms of latent class analysis (LC) subsets, LC1 (axillary–mammary–groin), LC2 (axillary–gluteal–groin), and LC3 (axillary–groin) constituted 25%, 41.7%, and 33.3% of the cohort, respectively.[13] All patients had previously undergone a median of 3 lines of therapy (range 2–5), with adalimumab in 100% and oral antibiotics in 95.8% of cases. The heterogeneity of therapeutic sequences is depicted in the Sankey diagram (Figure 1). Adalimumab discontinuation occurred in 17 cases (70.8%) due to therapy inefficacy and 8 cases (29.2%) due to side effects (i.e. psoriatic reactions, myalgias, and pain at the injection site). At therapy initiation, the overall median IHS4 was 18 (range 2–56), specifically 15 (range 2–27) for Hurley 2 and 30 (range 13–56) for Hurley 3 patients ($p = 0.03$). The median secukinumab drug survival was 16.0 months (*sd* 2.58), with 13 cases of drug discontinuation due to inefficacy and 1 case due to secukinumab-related side effects (headache) (Figure 2A). No differences on drug survival were detected in terms of Hurley stage ($p = 0.540$) nor LC classes at therapy start ($p = 0.656$) (Figure 2B, C). Considering the patients who reached the different follow-up evaluated periods, the highest HiSCR and IHS4-55 rates were recorded as 56.5% achievement at 6-months. The baseline IHS4 disease burden negatively correlated with achieving HiSCR-IHS4-55 (HR 0.88, 95% CI 0.79–0.98, $p = 0.021$), and patients with Hurley 2 were more likely to reach the endpoints compared to those with Hurley 3 ($p = 0.045$). Among the prior lines of therapies that preceded the initiation of secukinumab, the use of systemic steroids (recorded in 20.8% of patients at baseline) was negatively associated with drug survival (HR 3.47, 95% CI 1.09–11.05, $p = 0.035$) in univariate analysis. Conversely, achieving HiSCR-IHS4-55 was positively associated with drug survival, with an HR of 0.21 (95% CI 0.06–0.68, $p = 0.010$), irrespective of the timing. A trend in DLQI improvement was noted, yet without achieving statistical significance at any timepoint ($p = 0.081$) (Supplementary S1).

3 | CONCLUSIONS & PERSPECTIVES

This study investigates the real-life use of the anti-IL17 agent secukinumab in treating moderate-to-severe HS, evaluating its clinical effectiveness and long-term duration of benefit. To date, only few studies have delved into the real-world effectiveness of secukinumab, underscoring the necessity for thorough, extended evaluations. For instance, Prussick et al. observed that 55.5% (5/9) of their patients achieved HiSCR at week 16, with 67% (6/9) maintaining this outcome at week 24.[14] Similarly, Melgosa et al. found that among 23 patients, 73.9% (17/23) achieved HiSCR at week 16, with sustained rates of 71.4% at weeks 24, 36, and 52 of treatment.[15] More recently, Martora et al. reported significant improvements in severity assessment scales, including IHS4 and DLQI, at weeks 16 and 52, with HiSCR reaching 71.4%.[16] In this context, our investigation contributes additional evidence by extending the follow-up periods, leading to notable findings. Firstly, the attained maximal response rates (56.5% at 6 months) underscore the less-than-ideal effectiveness of this drug in practical

TABLE 1 Patients' characteristics.

Total patients				24 (100%)	
Gender male, *n* (%)				9 (37.5%)	
Family history positive for HS, *n* (%)				5 (20.8%)	
Comorbidities, *n* (%) • Smoke • Cardiovascular disease • Polycystic ovary syndrome • Psoriatic disease • Diabetes Mellitus • Psychiatric disease • Autoimmune disease				18 (75.0%) 18 4 2 6 2 2 3	
Age of HS onset (mean ± SD)				21.7 ± 9.3	
Age of HS diagnosis (mean ± SD)				34.5 ± 14.4	
Diagnostic delay in years (mean ± SD)				12.1 ± 11.1	
BMI (mean ± SD)				27.2 ± 4.9	
• 18.5–24.9				11 (45.8%)	
• 25–29.9				3 (12.5%)	
• 30–34.9				10 (41.7%)	
Prior lines of systemic treatment received (median, range)				2 (1–5)	
• Adalimumab				24 (100%)	
• Systemic Antibiotics • Clindamycin (+/− Rifampicin) • Tetracycline • β-lactams				23 (95.6%) 17 8 2	
• Oral retinoids				8 (33.3%)	
• Surgery				6 (25.0%)	
• Systemic Corticosteroids				5 (20.8%)	
• Anti-IL23 agent				1 (4.2%)	
Age at Adalimumab start (mean ± SD)				37.0 ± 15.0	
Weeks on Adalimumab (mean ± SD)				80.1 ± 40.0	
Secukinumab	T0	T3	T6	T9	T12
Reached FU*	24	24	23	22	21
Patients on Tx	24	24	20	14	12
Discontinuation	-	0	3	8	9
IHS4 score					
Mean (± SD)	21.2 ± 13.6	18.4 ± 12.5	14.6 ± 11.8	12.9 ± 11.1	18.3 ± 25.0
Median	18	19	11	10	9
HiSCR achievement, n (%)°	–	Achieved: 6 (25%) Not achieved: 18 (75%)	Achieved: 13 (56.5%) Not achieved: 10 (43.5%)	Achieved: 9 (40.9%) Not achieved: 13 (59.1%)	Achieved: 6 (28.5%) Not achieved: 15 (71,5%)
IHS4-55 achievement, n (%)°	–	Achieved: 2 (8.3%) Not achieved: 22 (91.7%)	Achieved: 13 (54.2%) Not achieved: 10 (43.5%)	Achieved: 7 (31.8%) Not achieved: 15 (68.2%)	Achieved: 6 (28.5%) Not achieved: 15 (71,5%)
DLQI Mean (± SD)	25 ± 3	21 ± 4	18 ± 4	15 ± 3	15 ± 3

Note: HS (Hidradenitis suppurativa), Tx (Therapy), SD (standard deviation), BMI (Body mass index), IHS4 score (number of nodules multiplied by 1 + number of abscesses multiplied by 2 + number of draining tunnels multiplied by 4. Total score ≤3: mild disease, 4–10: moderate disease, 11 ≥ severe disease), HiSCR (achievement defined as ≥ 50% reduction in inflammatory lesion count and no increase in abscesses or fistulas compared to baseline), IHS4-55 (achievement defined as ≥ 55% reduction in the IHS4 score), T0 (Time zero, Secukinumab first prescription), T3 (Time at 3 months), T6 (Time at 6 months), T9 (Time at 9 months), T12 (Time at 12 months). *Reached follow up (FU) refers to the time in study for each patient (i.e. time 'at-risk' in the drug survival analysis)°Achievement rates calculated as Intent-to-Treat (ITT) analysis (i.e. total cases of achievement over number of patients who reached the FU evaluation time).

scenarios. Specifically, while post-hoc analyses of the trials report that 76%–84% of patients showing a clinical response at week 16 maintain benefits at week 52, our real-life study reveals a more challenging scenario, with dropout rates exceeding 40% at the one-year mark.[5] Significantly, within our cohort, the predominant factor influencing the response to secukinumab is the baseline disease burden. No other

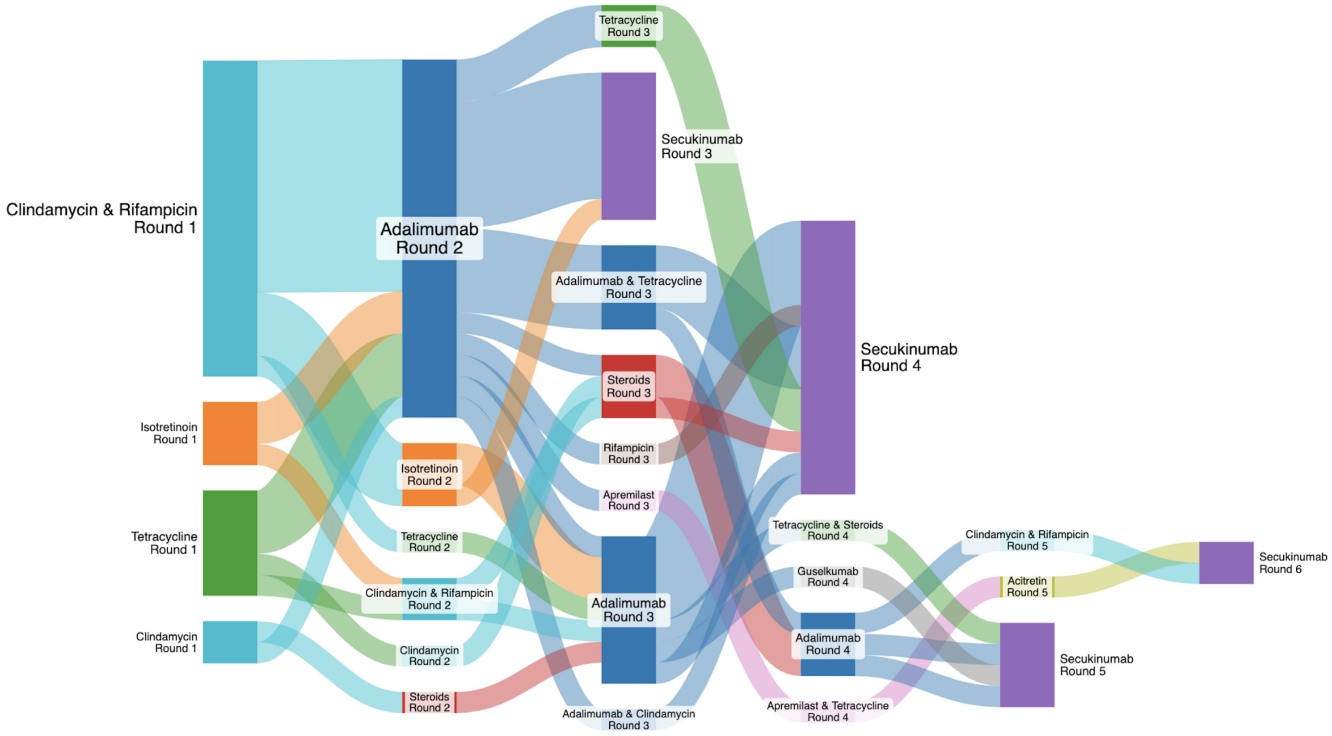

FIGURE 1 Sankey diagram of lines of systemic therapy prior to secukinumab.

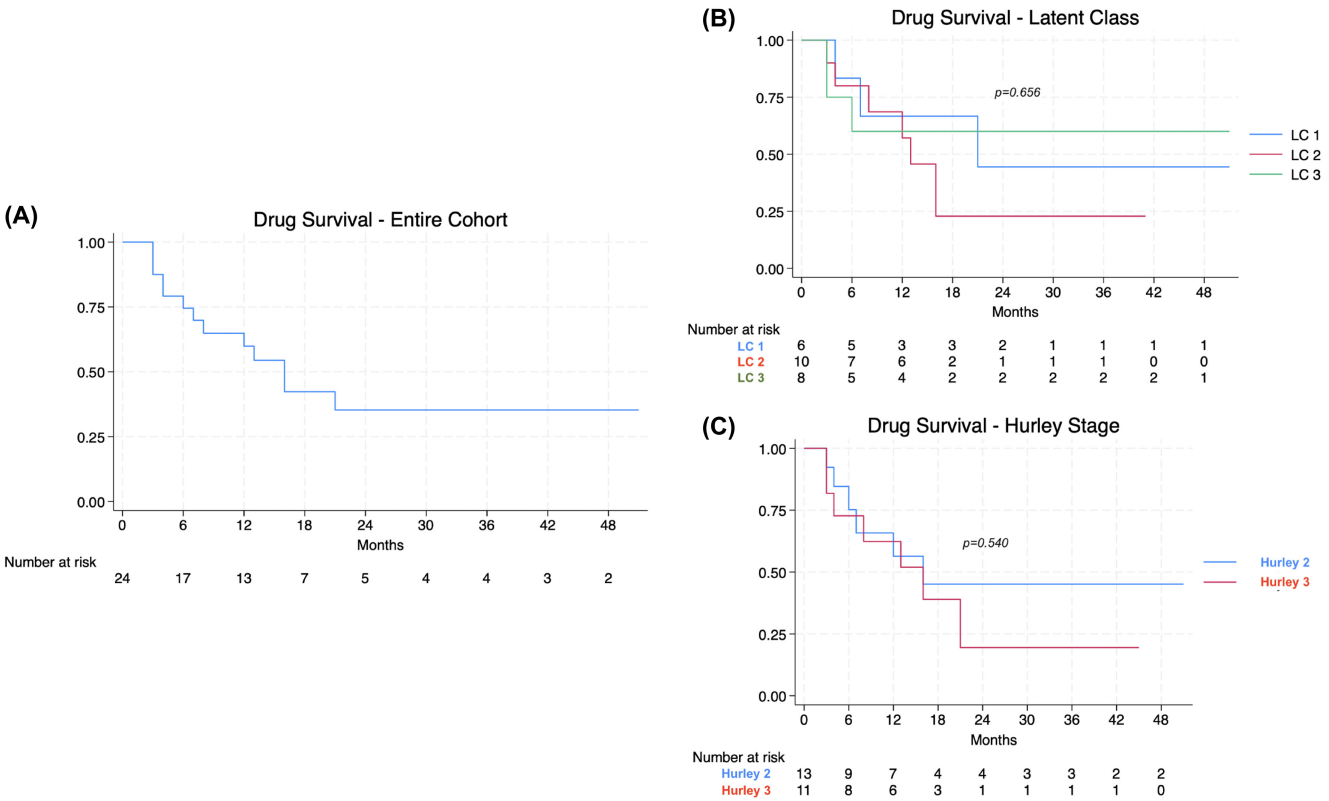

FIGURE 2 Secukinumab survival of the overall cohort, according to Hurley stage and LC classes.

clinical parameter, such as sex, smoking habit, or BMI demonstrates a predictive potential comparable to the baseline disease burden, underscoring its pivotal role in gauging treatment response. Conversely, previous administration of systemic steroids, whether alone or combined with other systemic medications, exhibited a detrimental impact on drug survival. This is likely attributed to a more resistant underlying

disease, despite no appreciable significant variances in baseline disease severity (i.e. mean IHS4 20 vs. 22, $p = 0.425$). Notably, resorting to oral steroids for rescue therapy did not demonstrate any improvement in patient outcomes. Secondly, the assessment of clinical benefit, if observed, occurs within the initial 6 months of therapy, making this timeframe as a crucial window for evaluating the effectiveness of the treatment. This potential benefit could be linked to the positive impact of the initial induction, characterized by the higher dosage administered during the initial 5 weeks. As for clinical phenotypes, the drug survival to secukinumab does not exhibit significant differences across various phenotypes within the LC categories.[13] Thirdly, the newly developed scoring system, IHS4-55, which was created to overcome the limitation of HiSCR in patients with an abscess-nodular count (AN) <3 accompanied by numerous draining tunnels, exhibits comparable discriminatory efficacy to HiSCR in capturing the optimal treatment response (Supplementary S2).[17] In our series, this phenomenon was observed 6 months into the therapy, despite displaying a slower rate of change during the initial 3 months of treatment. At last, there was only a modest impact on the improvement of patients' quality of life, with a mild benefit not reaching statistically significance. Although the study's drawbacks encompass a limited sample size and a monocentric design, the overall rates of response and drug survival depicted are noteworthy. These findings contribute valuable insights into the disparities between real-world scenarios and controlled clinical trials. For instance, while 76% of the patients enrolled in the SUNRISE and SUNSHINE were naïve to biologic therapy, 100% of the patients in our study were adalimumab-experienced.[5] This disparity underscores the importance of recognizing differing expectations in real-life scenarios among clinicians and patients. Metanalytic data proved that approximately half of patients with HS treated with biologics cease treatment by the first year of treatment, with comparable trends between anti-TNF, anti-IL17, and IL-23 agents.[18] Coherently, our data confirm that biologics in HS fall short in comparison their usage for psoriatic disease.[19] This disparity highlights the ongoing challenges in managing this disease, emphasizing the critical need for the development of integrated strategies aimed at targeting simultaneously distinct biologic pathways.[20–23] Given the urgency of identifying new predictive markers for treatment response to accurately target individuals who will benefit most from IL17 inhibition, translational research will be crucial in addressing this need in the near future.

AUTHOR CONTRIBUTIONS

G.R., F.R., P.Q., P.D., S.R. conceived and designed the presented work. G.R. wrote the manuscript with input from all authors. S.G., C.S., A.C. contributed to implementation of the research.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

The patients in this study gave written informed consent to publication of their case details.

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SUPPORTING INFORMATION

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

Supplementary S1. DLQI (Dermatology Life Quality Index), sd (standard deviation).

Supplementary S2. HiSCR (Hidradenitis Suppurativa Clinical Response), IHS4-55 (Reduction of at least 55% in the International Hidradenitis Suppurativa Severity Score System).

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