Real-world adherence to topical therapies in patients with moderate acne

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Background: Real-life data on topical treatments in daily practice in patients with moderate acne are poorly characterized.

Objective: To investigate the drug survival of topical treatments administered to patients with moderate acne in a daily practice.

Methods: Survival analysis was performed on subjects (Belgian university hospital and private practice outpatient dermatology patients) with moderate acne who received topical therapies according to the current published guidelines.

Results: A total of 1160 treatment series (1029 patients) were included, including benzoyl peroxide (BPO, n = 93), azelaic acid (n = 246), adapalene (n = 254), a fixed combination of adapalene 0.1% and BPO 2.5% (A/BPO, n = 264), and a fixed combination of clindamycin 1.2% and tretinoin 0.025% gel (Clin-RA, n = 303). The calculated overall median treatment duration of all drugs was 2 months. The probability of treatment discontinuation after only 3 months was 50%. Overall, the drugs were discontinued for the following reasons: controlled acne (9%), side effects (9%), ineffectiveness (52%), combination of side effects and ineffectiveness (3%), and other reasons (1%). Overall, 27% patients were lost to follow-up.

Limitations: The post hoc study design and generalizability limit interpretation of the data.

Conclusion: Overall, the median treatment duration of topical anti-acne therapies was short (2 months). The main reason for discontinuation was ineffectiveness. (JAAD Int 2021;2:109-15.)

Key words: acne; adapalen; benzoyl peroxide; clindamycin; drug survival; topical.

INTRODUCTION

Acne vulgaris is defined as a chronic disease because of its long duration and pattern of recurrence or relapse. In contrast to the common perception of acne as a temporary problem affecting adolescents, in many patients, acne persists for several years.[1,2] The duration of acne varies from 3 months to 40 years, and for 80% of patients, the disease does not spontaneously regress until they are in their thirties.[1]

According to the current guidelines,[3] the use of various local anti-acne therapies, including benzoyl peroxide (BPO), azelaic acid, adapalene, a fixed combination of adapalene 0.1% and BPO 2.5% (A/BPO), a fixed combination of clindamycin and BPO, or a fixed combination of clindamycin 1.2% and tretinoin 0.025% gel (Clin-RA), is recommended for the treatment of moderate papulo-pustular acne. These guidelines are usually derived from 12- or 16-week randomized follow-up studies,[3-5] and more

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rarely 6-month maintenance therapy studies.[2,6,7] In these studies, the mean percentage reduction in the total lesion count usually does not exceed 80%.[2-6] For most patients, such therapies are usually not curative, and the chronic nature of acne may lead to inadequate adherence. However, little is known about the long-term outcomes of topical therapies among patients with moderate acne in a real-world setting.

Drug survival is defined as the probability that a patient will remain on a given drug, as discontinuation of therapy can occur for a number of reasons, the most common being a lack of efficacy, side effects, or controlled disease.[8-14] To our knowledge, this is the first study on drug survival in the context of topical treatment for patients with acne. We aimed to perform a detailed analysis of drug survival for topical therapies in a long-term daily practice cohort of patients with moderate acne.

CAPSULE SUMMARY

- The use of various topical anti-acne therapies is recommended for the treatment of moderate papulo-pustular acne.
- The median drug survival of topical anti-acne therapies is short, and the main reason for discontinuation is ineffectiveness.

PATIENTS AND METHODS

Patient selection criteria

This study was carried out at 3 centers, including a university hospital and 3 private practices, in Brussels, Belgium. It was approved by the local Ethics committee (Saint-Pierre University Hospital, Brussels, Belgium; ref. O.M. 007, CE/20-04-03) and was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the 1996 Declaration of Helsinki. We included 1029 patients with moderate papulo-pustular acne who had been treated with either BPO, azelaic acid, adapalene, A/BPO, or Clin-RA, according to the European guidelines.[3] The fixed combination of clindamycin and BPO was not considered because it is unavailable in Belgium. Topical antibiotic monotherapies were not considered because their use is no longer supported by guidelines. All patients who began treatment with these therapies between January 2010 and December 2019 were included. The data lock for this study took place in December 2019. We excluded patients who were treated with these drugs as part of a clinical trial. We also excluded patients who were previously treated with systemic anti-acne drugs. The patients' medical records were reviewed, and the following information was recorded: sex, age, duration of anti-acne treatment, and reason for discontinuation of anti-acne treatment. The primary outcome was the drug survival associated with each of those drugs.

Because a patient could have received 2 or more topical anti-acne treatments during the study period, the same patient could have been included more than once in the analysis for each different treatment series with a different anti-acne agent. An event was defined as treatment termination if no prescription for the agent was claimed for 365 days.

Drug survival and statistical analysis

Five drug survival events were defined and analyzed separately: (i) discontinuation overall (encompasses ii, iii, iv, and v); (ii) discontinuation owing to controlled acne; (iii) discontinuation owing to side effects; (iv) discontinuation owing to ineffectiveness, (iii and iv) discontinuation owing to side effects plus ineffectiveness, and (v) discontinuation for reasons other than the event of interest (e.g. non-compliance, pregnancy), as in a previously published report.[9] In the overall analysis (i), subjects were censored (i.e., no event during the observation time) when still active at the moment of data lock or when lost to follow-up (LTFU). All side effects leading to treatment discontinuation were collected.

We present patient characteristics as frequencies with percentages for categorical variables and as means with standard errors for continuous variables. Differences in continuous variables were compared between more than 2 groups using analyses of variance with one grouping factor (kind of drug), followed by the Sidak or Dunnett T3 multiple comparisons test when required, according to the results of the Levene test for homoscedasticity.

Differences in qualitative variables were compared between groups using Pearson exact chi-square test. Kaplan-Meier plots were used to present survival curves, which were compared using the log-rank test. "Event" was defined as cessation of therapy. The reported estimated medians are the survival durations for which the survival probability is 50%, according to the Kaplan-Meier curves. A logistic binary regression analysis was used to determine whether age, sex, duration of acne, and use of previous anti-acne treatments were significant predictors of treatment dropout. Comparisons were performed using 2-sided tests, with P values $< .05$ considered to indicate statistical significance. All statistical tests were performed using the IBM-SPSS

Abbreviations used:

A/BPO:	fixed combination of adapalene 0.1% and BPO 2.5%
BPO:	benzoyl peroxide
Clin-RA:	fixed combination of clindamycin 1.2% and tretinoin 0.025% gel
LTFU:	lost to follow-up
RCT:	randomized controlled triaL

(version 26.0) (IBM Corp, Armonk) and MedCalc V14 (Ostend) statistical software packages. Missing data were excluded from the relevant analyses.

RESULTS

Patient and treatment characteristics

A total of 1029 patients aged 22.8 ± 0.3 years (mean ± standard error) who received 1160 topical anti-acne treatment series were included in the study (Table I). Of these, 658 (64%) were female, and 698 (68%) were naive for anti-acne therapies. The 1160 treatment series included 93 cases treated with BPO, 246 cases with azelaic acid, 254 cases with adapalene, 264 cases with A/BPO, and 303 cases with Clin-RA. The most commonly prescribed topical anti-acne treatment in our series was Clin-RA, which was administered 303 times (26.14% of all treatments). Generally, the patient characteristics were comparable across the 1160 treatments (P = .040), although the ages were globally different due to the significantly higher ages of patients treated with BPO patients (24.96 ± 0.90 years) and adapalene (21.81 ± 0.52 years; P = .027).

Reasons for discontinuation of treatment

Although an event in a drug survival analysis indicated that the drug was no longer successful in other studies, anti-acne treatment can also be discontinued for controlled acne. This requires the interpretation of data from another perspective, as this event favors the effectiveness of the treatment.

In December 2019, the time point of data lock, 85 (7%) topical anti-acne therapies remained active and 1075 treatments had been discontinued (93%). The calculated overall median treatment duration of all drugs was 2 months, with durations of 3, 2, 2, 2, and 2 months for BPO, azelaic acid, adapalene, A/BPO, and Clin-RA, respectively. Overall, 108 (9%) treatments were discontinued because of controlled acne. The reason for discontinuation was ineffectiveness in 545 (52%) cases and side effects plus ineffectiveness in 32 cases (3%). Furthermore, 318 (27%) cases were LTFU and 15 (1%) treatments were stopped for other reasons (e.g., cost, pregnancy). Side effects were the reason for discontinuation of treatment in 90 (9%) cases (Table I). Skin irritation/dryness (6.6%), eczema (1.1%), and acne exacerbation (0.0008%) were the reported side effects leading to discontinuation of treatment (Table II).

Controlled acne was more frequently associated with Clin-RA and less frequently with BPO and A/BPO. Throughout the study, the main reason for the discontinuation of BPO, azelaic acid, adapalene, A/BPO and Clin-RA was insufficient efficacy. Side effects were the second most common reason for the discontinuation of BPO and of A/BPO, whereas controlled acne was the second most common reason for the discontinuation of azelaic acid, adapalene, and Clin-RA. Azelaic acid was associated with fewer side effects than BPO (P = .036) and A/BPO (P = .008).

Drug survival analysis

Figure 1 shows the overall durations of treatment with BPO, azelaic acid, adapalene, A/BPO, and Clin-RA in patients with moderate acne. The overall probability of treatment discontinuation after only 3 months was 50%, and 50% discontinuation occurred at 3, 2, 9, 10, and 3 months for BPO, azelaic acid, adapalene, A/BPO, and Clin-RA, respectively.

DISCUSSION

Drug survival is defined as the time period of treatment with a certain drug until cessation. It is a well-recognized measure that encompasses factors such as effectiveness, patient adherence and compliance, adverse events, patient expenditures, and physician preferences in a real-world setting.[10,11] In dermatology, drug survival has been mainly studied in the field of psoriasis to quantify the loss of efficacy of biologics over time.[8,11] It has also been investigated in other diseases such as atopic dermatitis, hand eczema, and scleroderma.[9,12,13] One study recently showed that spironolactone has an extended drug survival in female patients with moderate-to-severe acne.[14]

In this retrospective study, we presented real-life data on the drug use and survival of patients treated with local anti-acne therapies, including BPO, azelaic acid, adapalene, A/BPO, and Clin-RA, which are recommended for the treatment of moderate papulopustular acne.[3] Topical antibiotics alone were not considered, as they are no longer recommended anti-acne options.[3,15] Drug survival is determined by the occurrence of an event indicating that a drug is no longer successful. However, topical anti-acne treatment can also be discontinued because of controlled acne. This requires the interpretation of data from another view because the discontinuation of treatment because of controlled acne is an event

Table I. Patient and treatment characteristics

*	BPO (n = 93)	Azelaic acid (n = 246)	Adapalene (n = 254)	A/BPO (n = 264)	Clin-RA (n = 303)	All therapies confounded (n = 1160)
Patient characteristics						
Male, n (%)	49 (53)	44 (18)	110 (43)	85 (32)	133 (44)	371 (36)
Mean age at treatment, years (SEM)	25.1 (0.9)	22.6 (0.6)	21.8 (0.5)	22.6 (0.4)	22.4 (0.5)	22.8 (0.3)
Mean duration of acne, months (SEM)	71.3 (7.8)	53.0 (5.0)	57.4 (4.6)	70.0 (4.5)	58.0 (4.0)	60.9 (2.4)
Treatment status at the moment of data lock[†, ‡]						
Active, n (%)	3 (3)	27 (11)	9 (4)	11 (4)	35 (12)	85 (7)
Discontinued, *n* (%)	90 (97)	219 (89)	245 (96)	253 (96)	268 (88)	1075 (93)
Drug duration						
Median calculated drug duration, m	3	2	2	2	2	2
Controlled acne, n (%)	1 (1)	30 (12)	24 (9)	12 (5)	41 (14)	108 (9)
Side effects, n (%)	14 (15)	8 (3)	21 (8)	27 (10)	20 (7)	90 (9)
Ineffectiveness, n (%)	55 (60)	111 (45)	137 (54)	142 (54)	100 (33)	545 (52)
Side effects plus ineffectiveness, n (%)	4 (4)	4 (2)	5 (2)	13 (5)	5 (2)	32 (3)
Other (non-compliance, pregnancy, cost), n (%)	0 (0)	2 (1)	4 (2)	3 (1)	6 (2)	15 (1)
Lost to follow-up, n (%)	21 (23)	69 (28)	62 (24)	61 (23)	105 (35)	318 (27)

BPO, Benzoyl peroxide; *A/BPO*, fixed combination of adapalene 0.1% and BPO 2.5%; *Clin-RA*, fixed combination of clindamycin 1.2% and tretinoin 0.025% gel; *SEM*, standard error of the mean.
*Values are given as n (%) unless otherwise indicated.
[†]Data lock occurred in December 2019.
[‡]Patients can be successively treated with different drugs. A single patient can be categorized by side effects and also by the lack of efficacy of the same drug.

Table II. Side effects reported as reasons for discontinuation of BPO, azelaic acid, adapalene, A/BPO and Clin-RA

*	BPO (n = 93)	Azelaic acid (n = 246)	Adapalene (n = 254)	A/BPO (n = 264)	Clin-RA (n = 303)	All therapies confounded (n = 1160)
Side effect as reason for discontinuation, n (%)						
Dryness	8 (8.6)	3 (1.2)	7 (2.8)	6 (2.3)	11 (3.6)	35 (3.0)
Irritation	5 (5.3)	5 (2)	11 (4.3)	14 (5.3)	7 (2.3)	42 (3.6)
Eczema	2 (2.1)	0 (0)	2 (0.8)	7 (2.7)	2 (0.7)	13 (1.1)
Acne exacerbation	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	1 (~0)

BPO, Benzoyl peroxide; *A/BPO*, fixed combination of adapalene 0.1% and BPO 2.5%; *Clin-RA*, fixed combination of clindamycin 1.2% and tretinoin 0.025% gel.
*Values are given as n (%) unless otherwise indicated.

that favors the effectiveness of topical anti-acne treatment. Therefore, in assessing the effectiveness of topical anti-acne treatment by drug survival, the reason for discontinuation of treatment is very important. The calculated overall median treatment durations of all drugs, BPO, azelaic acid, adapalene, A/BPO, and Clin-RA were 2, 3, 2, 2, 2, and 2 months, respectively. The reasons for the discontinuation of treatment were controlled acne (9%), side effects (9%), ineffectiveness (52%), side effects plus ineffectiveness (3%), and other reasons (1%).

Topical anti-acne treatment was discontinued because of controlled acne in a minority of patients (9%). This may contradict the results of a multitude of clinical studies demonstrating that topical anti-acne therapies are safe and potent drugs in the treatment of moderate acne vulgaris.[3,16,17] However, to be clinically useful, these results must also be generalizable to patients in a daily practice setting. There are several examples in the literature of the low generalizability of trial results with respect to daily practice.[9,18] For example, the external validity of clinical study results has also been investigated in the treatment of psoriasis and rheumatoid arthritis with biologics.[19] The outcomes of psoriasis treatment in daily practice were shown to be less effective than the results from randomized controlled trials (RCTs).[19] There are several possible explanations for the difference between daily practice and trial results.[9] RCTs are restricted by their inclusion criteria and size and are powered for primary efficacy outcomes, resulting in a low external validity for

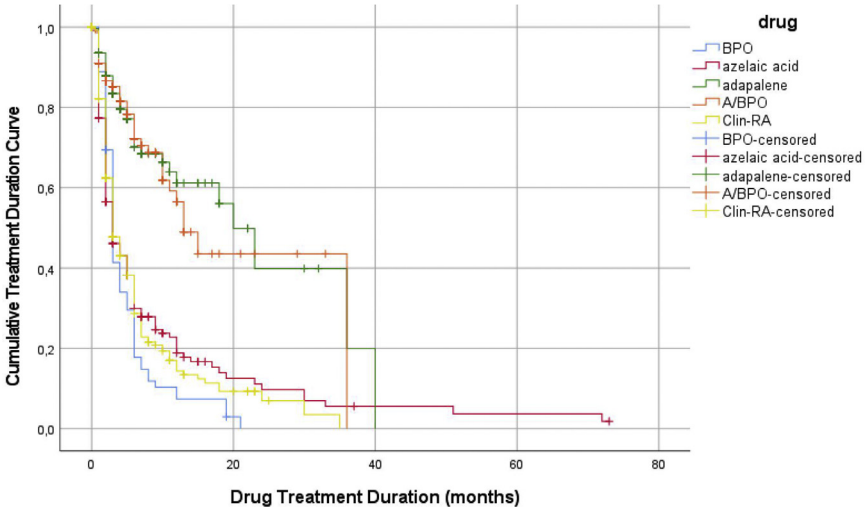

Fig 1. Drug survival of BPO, azelaic acid, adapalene, A/BPO, or Clin-RA. *BPO*, Benzoyl peroxide; *A/BPO*, fixed combination of adapalene 0.1% and BPO 2.5%; *Clin-RA*, fixed combination of clindamycin 1.2% and tretinoin 0.025% gel.

"real-world" populations. The external validity of a RCT also depends on whether the outcomes are clinically relevant. The main outcome in clinical trials on acne is often the mean/median decrease in the lesion counts in the total group after relative to before treatment, or the difference in the mean/median decrease in lesion counts between 2 treatment groups at fixed time points. However, mean decreases give no information about the individual response rates. Another factor influencing the external validity of RCTs is the limited duration of treatment. RCTs are costly and usually involve a relatively brief treatment period with limited follow-up. Whether the initial response is a good predictor of the long-term benefit is unknown. Most typically, acne is not an acute disease but rather a long-lasting condition associated with great social and/or psychological burdens. Likely, for most patients, the long-term application of a moderately active local treatment is not an optimal option. Controlled acne was more frequently associated with Clin-RA and less frequently with BPO and A/BPO. Data from clinical trials suggest that Clin-RA is as effective as A/BPO[20] but causes significantly less skin irritation.[21]

In our daily practice cohort, 9% of the treatments were discontinued because of side effects. The most common adverse events leading to the cessation of therapy were dryness/irritation and eczema. BPO and A/BPO more commonly led to treatment discontinuation because of local adverse events than other drugs, which supports the previous findings from RCTs showing that BPO and topical retinoids are associated with a higher irritative potential.[22] Our real-world data also show that azelaic acid was associated with fewer side effects than BPO and A/BPO. These data are also in accordance with the results of RCTs.[3]

In our study, discontinuation because of ineffectiveness was registered in 52% of the cases. This percentage is much higher than that reported in clinical trials. Given the short durations of most clinical trials, patients are frequently motivated to continue treatment until the end of the trial, despite ineffectiveness.[9]

Many other factors, such as disease severity, physicians' preferences, and the availability of other treatment options, also influence drug survival. Treatment is more likely to be continued despite a moderate response or the presence of side effects when no other treatment options are left. Many patients are aware of the availability of more efficient treatments, such as isotretinoin. Particularly, topical anti-acne drug survival might be lower because of the availability of isotretinoin. The cost of medications may also encourage patients to consider discontinuing therapy. In our study, only a minority of patients (≤1%) discontinued treatment for this reason, but it remains possible that price acts synergistically with other factors to decrease the drug survival of topical anti-acne therapies.

Finally, a significant proportion of the patients was LTFU or reported low compliance with therapy. A previous review showed that adherence to topical anti-acne therapy may be limited in RCTs (75%).[23] Differences in dropout/LTFU rates between clinical trials ("ideal" conditions) and daily practice ("usual"

conditions) is a well-known phenomenon.[24] Our data showing the low drug survival of topical anti-acne therapies support previous studies which showed that adherence to acne medications was often poor and was correlated with the occurrence of side effects and lack of improvement.[25,26]

This study has several limitations due to its retrospective, observational design. Selection bias is unavoidable in daily practice, as patients receive treatment based on both their own and the physicians' preferences, which is one of the strengths of daily practice studies.[9] Because this was not an RCT, the patients' characteristics (including the number of previous treatments and duration of acne) differed. Consequently, the between-drug comparisons should be done with caution. The generalizability of our results was limited by the local recruitment of the patients. For instance, there were no patients treated with the fixed combination of clindamycin and BPO and few treated with BPO alone, which may reflect the availability of the medication and/or physicians' preferences. Nevertheless, to our knowledge, this study is the first to investigate the drug survival of topical therapies for the management of moderate acne in a real-world setting.

In conclusion, we showed that the median overall drug survival rate for topical treatments in patients with moderate acne in daily practice was low (2 months), which contrasts with the chronic character of acne. Ineffectiveness (or perceived ineffectiveness) was the most common reason for discontinuation.

Conflicts of interest

None disclosed.

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