How Much Do We Know about Maintaining Treatment Response after Successful Acne Therapy? Systematic Review on the Efficacy and Safety of Acne Maintenance Therapy

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Key Words

Acne vulgaris · Maintenance · Systematic review · Recurrence · Adapalene · Benzoyl peroxide · Tazarotene · Isotretinoin

Abstract

After cessation of successful initial acne therapy, patients often experience flares. Consecutive maintenance treatment after successful induction therapy is promoted by guidelines; however, little is known about the efficacy/safety of different maintenance regimens. A systematic review on acne maintenance treatments was conducted. We identified 5 randomized controlled trials [RCTs; adapalene vs. vehicle or vs. no treatment (3 RCTs), adapalene/benzoyl peroxide (BPO) vs. vehicle, combination/monotherapy of minocycline (systemic)/tazarotene/placebo] and 3 non-RCTs on systemic isotretinoin, adapalene/BPO and azelaic acid. The results of adapalene versus vehicle/no treatment varied depending on the reported outcome. The ‘number of patients maintaining at least 50% improvement’ counting inflammatory lesions/non-inflammatory lesions with adapalene was superior to vehicle (risk ratio, RR 1.24, 95% confidence interval, CI 1.08–1.43/RR 1.34, 95% CI 1.18–1.59). However, no significant differences were found in 2 of 3 RCTs for maintaining

‘clear/almost clear’ or ‘mild acne’ or on the global grading score. For the combination regimens of minocycline/tazarotene/placebo, no significant differences were found. Adapalene/BPO was superior to vehicle counting inflammatory lesions/non-inflammatory lesions (RR 1.61, 95% CI 1.31–1.99; RR 1.80, 95% CI 1.44–2.26). Due to the scarcity of studies, few conclusions can be drawn. More homogeneous outcome measures and specific maintenance study designs may lead to more robust findings.

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Introduction

Acne is a very frequent skin disease, which, depending on its severity, can have a severe impact on the patients’ quality of life. In contrast to the common perception of acne being a temporary pre-adolescents’ and mostly cosmetic problem, in many patients acne persists for several years. It may progress to acne tarda, which is present in up to 40% of patients [1]. Even after resolution of the inflammatory active acne period, many patients are left with a significant amount of scarring, which affects self-esteem and can cause additional psychological distress later on [2].

Fig. 1. Definition of responder population for maintenance therapy.

Table 1. Inclusion criteria

PICOS	Description
Population	Adolescents and adults Inclusion of patients who achieved a clearly defined treatment goal (e.g. reduction in lesion count by 60%) before entering into the reported maintenance study
Intervention	Approved systemic and topical interventions for acne (other than anti-androgens and laser and light therapies)
Comparison	With another drug and/or placebo, or without comparison
Outcome	Efficacy and safety/tolerability outcomes
Study design	Randomized controlled trial or controlled interventional study with a minimum duration of 12 weeks; at least 10 participants per study arm

Most of the available studies have focused on induction therapy, and currently available systematic reviews have evaluated efficacy, safety and onset of action of anti-acne treatments. Guidelines include maintenance therapy but only based on an ‘expert opinion approach’. Thorough systematic review methods have yet to be utilized to inform these decisions.

In contrast to its relevance in daily practice, only few attempts have been made to identify optimal maintenance

regimens. Questions such as how to best maintain treatment response after successful systemic isotretinoin or antibiotics therapy or how to continue on an initially successful but strongly irritating topical therapy with a better tolerable maintenance treatment need to be answered.

This systematic review summarizes the current evidence with regard to acne maintenance therapy. We aimed to:

- 1 provide a concise overview of published studies,
- 2 evaluate the quality of current studies, and
- 3 if suitable, combine outcome measures in meta-analyses.

Methods

For further details, see the supplementary materials (for all on-line suppl. material, see www.karger.com/doi/10.1159/000446069) [3–5] (fig. 1; table 1).

Results

Our initial search found 436 records. After removing duplicates, 280 records were left. By scanning reference lists another 4 and by auto-alerts (last search July 15, 2015) another 17 records were identified (fig. 2). Titles and abstracts of 301 records were screened for inclusion/exclusion; 264 publications did not meet the predefined inclusion criteria. Twenty-seven full-text studies were excluded due to: no definition/evaluation of ‘responder’ (14), no original data (7), no relevant outcome data (2), no maintenance treatment (2), full text not obtainable (1), and less than 10 patients (1). We included 8 studies (data published in 10 different publications) reporting on adapalene gel 0.1%, adapalene 0.1%/benzoyl peroxide (BPO) 2.5% fixed combination, tazarotene gel 0.1% and minocycline 100 mg as well as azelaic acid (AA) 20%.

Five studies were randomized controlled trials (RCTs), which will be described first. A summary of the 3 non-randomized studies and data on relapse, adverse events and risk of bias will be presented for all included studies thereafter.

Randomized Controlled Trials

Five RCTs including a total of 983 participants (from 36 to 127) with a mean age range of 17.8–19.1 years and 43–64% female participants at baseline of the maintenance phase were included (table 2). The skin type/ethnic

Fig. 2. Flow chart of record selection.

background, if stated, was: 100% Mongoloid [6], 87.5% Caucasian and 8.8% black [7], 75% white and 15.5% black [8], 45% white and 36% black [9]. Each of the included maintenance RCTs was a follow-up of an initial RCT on induction therapy.

Therapies and reported outcome measures differed widely, hence pooling was only appropriate in 1 case. The timing of outcome assessment varied from 12 to 24 weeks. Results for each drug are reported in the next section.

Adapalene Compared to Placebo

Three placebo-controlled RCTs [6–8] evaluated adapalene 0.1% gel applied once daily (table 2). The RCTs included responders who had achieved ‘at least moderate

improvement’ during the induction therapy phase (assessed using different scales in each study, see below).

In 2006, Thiboutot et al. [8] had conducted a 12-week induction RCT comparing adapalene 0.1% gel plus doxycycline 100 mg compared to doxycycline 100 mg alone. Responders, those who achieved at least moderate improvement, were then re-randomized to receive adapalene gel 0.1% q.d. or vehicle q.d. maintenance treatment for 16 weeks. The authors report a global severity assessment on a 6-point scale (from clear to worse) with 27% of participants still being ‘clear/almost clear’ in the adapalene arm and 16% of participants in the vehicle arm at the end of the maintenance phase. Statistically, no significant difference was found between the two groups

Table 2. Study characteristics of included RCTs

Maintenance phase				Induction phase		Inclusion criteria at induction				Outcome maintenance: lesion count, safety						
study	drug	dura- tion, weeks	res- pon- ders, n	definition of responder	drug	n	type of study	dura- tion, weeks	severity	severity definition	age, years	n	definition of outcome	results	safety	
Alirezai et al. [7], 2007	Adapalene gel 0.1% q.d. in the evening for 12 weeks	12	73	At least moderate improvement from baseline (7-point scale: worse; no change/slight change 1–24% improvement; moderate	Lymecycline 300 mg q.d. in the morning and adapalene gel 0.1% q.d. in the evening for 12 weeks	242	RCT	12	Moderate to moderately severe	4–10 Leeds Revised Acne Grading System; ≥15 IL (facial, ≤3 NO) and ≥20 NIL (facial)	12–30	12	73	Percentage of subjects maintaining at least 50% improvement from previous combination study	IL 76.4% (n = 56) NIL 84.7% (n = 62)	4 patients with treatment- related AEs (headache 2, eczema 1, erythema 1)
	Vehicle q.d. in the evening for 12 weeks		63	improvement 25–49%; marked improvement 50–74%; almost clear 75–99%; clear 100%)	Lymecycline 300 mg q.d. in the morning and vehicle q.d. in the evening for 12 weeks							63		IL 66.7% (n = 42) NIL 55.6% (n = 35)	0 treatment- related AEs	
Thiboutot et al. [15], 2005; Thiboutot et al. [8], 2006	Adapalene gel 0.1% q.d.	16	126	Moderate improvement from baseline (50%/ 6-point scale clear to worse)	Adapalene gel 0.1% and doxycycline 100 mg	238	RCT	12	Severe	≥15 IL, 15–100 NIL	12–30	16	126	Percentage of subjects maintaining at least 50% improvement from previous combination study	IL 74% (n = 93) NIL 71% (n = 89)	3 patients with treatment- related AEs
	Vehicle q.d.		127		Doxycycline plus vehicle	229							127		IL 57% (n = 72) NIL 55% (n = 70)	1 patient with treatment- related AEs
Zhang et al. [4], 2004	Adapalene gel 0.1% q.d.	12	122	At least moderate improvement (≥2 on scale from 1 = worse to 5 = clear)	Adapalene 0.1% q.d. and clindamycin phosphate 1% b.i.d.	150	RCT	12	Moderate to moderately severe, 10–50 IL facial, ≤3 NO and/or cysts, 20–150 NIL facial, global severity: II–III	Modified international acne grading system	12–35	12	122	Mean percentage reduction in lesion count	IL 41.7% NIL 40.8%	No AEs occurred
	No treatment		119		Clindamycin 1% b.i.d.	150							119		IL –97.1% NIL –87.7%	
Poulin et al. [11], 2011; Stein Gold et al. [16], 2010	Adapalene 0.1%/BPO 2.5% gel q.d.	24	123	≥50% global improvement	Doxycycline 100 mg q.d. and adapalene-BPO	232	RCT	12	Severe acne	Investigators Global Assessment grade 4 (6-point scale, 0 = clear, 5 = very severe)	12–35	12	123	Maintenance rate, percentage of subjects having ≥50% of improvement from prior therapy	IL 82.1% (n = 101) NIL 83.7% (n = 103)	5 patients with treatment- related AEs; 76.7% erythema, 70.8% scaling, 73.3% dryness, 78.3% burning
	Vehicle q.d.		120		Doxycycline 100 mg q.d. and vehicle	227							120		IL 61.7% (n = 74) NIL 60% (n = 72)	1 patient with treatment- related AEs; 83.5% erythema, 92.2% scaling, 88.7% dryness, 92.2% burning

Table 2 (continued)

Maintenance phase				Induction phase			Inclusion criteria at induction			Outcome maintenance: lesion count, safety					
study	drug	dura- tion, weeks	res- ponders, n	definition of responder	drug	n	type of study	dura- tion, weeks	severity definition	age, years	dura- tion, weeks	n	definition of outcome	results	safety
Leyden et al. [9], 2006	Tazarotene gel 0.1% every evening plus PBO capsule b.i.d.	12	36	Investigator-rated improvement of ≥75% from baseline (categories: 100%, approx. 90%, 75%, 50%, 25%, no change or worsening)	Tazarotene gel 0.1% every evening (pea-sized amount) plus minocycline capsule b.i.d.	189	RCT	12	Moderately severe to severe	≥12	12	27	Maintaining ≥70% of the reduction in NIL/IL attained in the initial treatment phase	IL 67% (n = 18) NIL 81% (n = 22)	0 treatment- related AEs
	Vehicle gel each evening plus 100 mg minocycline hydrochloride capsule b.i.d.		37						Acne vulgaris, 10–100 facial NIL, 25–60 facial IL, ≤2 nodular cystic lesions			31		IL 84% (n = 26) NIL 71% (n = 22)	
	Tazarotene gel 0.1% every evening plus 100 mg minocycline capsule b.i.d.		37									31/30		IL 77% (n = 24) NIL 90% (n = 27)	

b.i.d. = Twice daily; NIL = non-inflammatory lesions; IL = inflammatory lesions; NO = nodules; AEs = adverse events; q.d. = once daily.

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with respect to the global severity assessment (risk ratio, RR 1.18; confidence interval, CI 0.77–1.82).

In 2007, Alirezei et al. [7] had initially compared adapalene gel 0.1% plus lymecycline 300 mg to lymecycline 300 mg plus vehicle. Responders, those who achieved at least moderate improvement after 12 weeks, entered a maintenance RCT whereby adapalene 0.1% gel q.d. was compared to vehicle gel q.d. Alirezei et al. stated that after 12 weeks of maintenance treatment, based on the Leeds Revised Acne Grading system of O'Brien et al. [10], the percentage of patients with 'mild acne' remained the same in the adapalene group (from 86.3 to 82.2%) but decreased slightly in the vehicle group (from 76.2 to 68.3%). No statistically significant difference could be found with regard to the grading system (RR 1.29, CI 0.99–1.47).

In contrast to the lack of statistical significance with respect to the grading used in the studies by Thiboutout et al. [8] and Alirezei et al. [7], the pooled effect of adapalene versus vehicle on the 'number of patients maintaining at least 50% improvement achieved in the initial study' was statistically significant based on inflammatory (IL) and non-inflammatory lesion (NIL) count [7, 8] (fig. 3).

In 2004, Zhang et al. [6] had compared adapalene 0.1% gel plus clindamycin phosphate 1% versus clindamycin 1% during a 12-week induction treatment RCT. Responders, those who achieved at least moderate improvement, were rerandomized to adapalene 0.1% gel q.d. or no treatment during the maintenance phase. Zhang et al. reported that 67.2% of patients in the adapalene group and 4.2% of patients in the placebo group reached 'global improvement' after 24 weeks (further improved or much improved/clear on a scale from –2 = total relapse to 2 = much improved/clear). A mean percentage reduction in total lesion count of 41.6% in the adapalene group and an increase of 92.1% in the placebo group were reported.

Adapalene plus BPO Compared with Vehicle

In 2010, Poulin et al. [11] had initially compared doxycycline plus BPO versus doxycycline monotherapy. Responders (those with ≥50% global improvement) were rerandomized to the fixed combination adapalene 0.1%/BPO 2.5% gel q.d. compared to vehicle q.d. as maintenance treatment. A statistically significant difference was found at 12 weeks based on IL count (RR 1.33, CI 1.13–1.57) and NIL count (RR 1.67, CI 1.38–2.04). This effect was larger after 24 weeks of maintenance treatment (IL count: RR 1.61, CI 1.31–1.99; NIL count: RR 1.80, CI 1.44–2.26). The authors also report that 70.70% of participants in the adapalene-BPO group had the same or a

Fig. 3. Forest plot of pooled effect (risk ratio) of adapalene versus vehicle: number of patients maintaining $\geq 50\%$ improvement based on IL (**a**) and NIL (**b**) counts. M-H = Mantel-Haenszel test.

better investigators' global assessment score (from 0 = clear to 5 = very severe) than at baseline maintenance compared to 34.20% of patients in the placebo group (RR 2.07, CI 1.58–2.72). Relapse was reported for day 56 in the vehicle group and day 175 in the treatment group. It had been defined as: the time when less than 50% improvement in 25% of participants or an investigators' global assessment score below baseline was achieved.

Tazarotene plus Minocycline

In 2006, Leyden et al. [9] conducted a maintenance RCT with patients who had successfully completed induction treatment with tazarotene 0.1% gel plus minocycline 100 mg and achieved at least 75% global improvement. Patients were then randomized into three groups: tazarotene gel 0.1% every evening plus a placebo capsule twice a day (b.i.d.), or vehicle gel every evening plus minocycline hydrochloride 100 mg capsules b.i.d., or tazarotene gel 0.1% every evening plus minocycline 100 mg capsules b.i.d.

No significant differences could be found with regard to the number of patients maintaining at least 70% improvement comparing tazarotene alone with minocycline alone (based on IL count: RR 0.79, CI 0.58–1.08; NIL count: RR 1.15, CI 0.86–1.53), or tazarotene alone versus tazarotene plus minocycline (based on IL count: RR 0.86, CI 0.62–1.19; NIL count: RR 0.91, CI 0.73–1.12) or minocycline alone versus tazarotene plus minocycline (based on IL count: RR 1.08, CI 0.86–1.38; NIL count: RR 0.79, CI 0.61–1.02).

Other Included Studies

Three additional 12-week non-randomized studies were included (table 3). Note that all of these studies reported only descriptive results. The studies differed in previously used therapies and methods of re-assignment/further treatment following the induction phase. These studies had recruited 261 participants. In 2013, Bettoli et al. [12] reported maintenance baseline data (mean age 21.2 years, range 13–38, 47.83% women, $n = 70$). In 2011,

Table 3. Study characteristics of included non-randomized studies (concerning the maintenance phase only)

Maintenance phase				Induction phase		Inclusion criteria at induction			Outcome: lesion count, safety							
study	drug	duration	responders, n	definition of responder	drug	n	type of study	duration	severity	severity definition	age for inclusion, years	duration n	definition results of outcome	safety		
Bettoli et al. [12], 2013	Adapalene gel 0.1% and BPO 2.5% fixed combination q.d.	12 weeks	69	Treatment until complete clearance (=acne grade 0.1 and no more lesions) and 1 further month	Oral isotretinoin daily dose ≤0.2 mg/kg, increased by 5 mg every 2 weeks	70 consecutive patients	Prospective cohort, non-comparative	Until clearance plus 1 month	Moderate to moderately severe	4–10 Leeds Revised Acne Grading System; ≥15 IL (facial, ≤3 NO) and ≥20 NIL (facial)	12–30	Lesion count was not reported	0 treatment-related AEs			
Gollnick et al. [13], 2001	AA 20%	3 months	41 (due to modification of inclusion criteria n = 26)	Number of deep IL had decreased by ≥75%, and efficacy of treatment was rated by patients as 'very good'	20% AA cream b.i.d. plus oral minocycline 50 mg b.i.d.	50	RCT	6 months	Severe inflammatory grade 4, ≥2 deep facial inflammatory lesions and other papules/pustules	Leeds grading scale	>16	3 months	26	Reduction in median lesion count	NIL from 13 to 17 IL from 3 to 7	2 patients reported mild burning or stinging
	Patients from the oral isotretinoin group did not receive any further maintenance treatment		30 (due to modification of inclusion criteria n = 26)		Oral isotretinoin (0.8 mg/kg 1st month, then 0.7 mg/kg 2nd month, then 0.5 mg/kg 3rd month and 0.5 mg/kg 4th–6th months q.d.)	35						26			NIL from 8 to 7 IL remained 2	
Meigel et al. [14], 1983	Isotretinoin 0.2 mg/kg b.w.	12 weeks	34	Reduction in lesion >2/3; after 12 weeks	Isotretinoin 0.2 mg/kg b.w.	51	Open, non-randomized study	12 weeks	Severe acne conglobata	n.s.	n.s.	12 weeks	n.a.	75% improvement in IL and	n.a.	10% of patients reported mild loss of hair, higher incidence of myalgia in the higher dose groups; very rarely reported: tiredness, headache, increased appetite ¹
	Isotretinoin 0.2 mg/kg b.w.		53	patients received the same or a smaller dose; all others received the same or a higher dose (only patients with reduced dose considered here)	Isotretinoin 0.5 mg/kg b.w.	68						52		NIL	72.5%	
	Isotretinoin 0.5 mg/kg b.w.		11									n.a.			n.a.	
	No treatment		27			79						26			91.6%	
	Isotretinoin 0.2 mg/kg b.w.		41									39			85.4%	
	Isotretinoin 0.5 mg/kg b.w.		2									n.s.			n.s.	

b.w. = Body weight; NO = nodules; n.s. = not stated; n.a. = not applicable. ¹ It was not possible to report numbers for just the patients in the lower dose groups of interest.

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Fig. 4. Risk of bias of included RCTs.

Gollnick et al. [13] conducted a study with just men, and in 1983 Meigel et al. [14] provided no sociodemographics. Ethnic background or skin type were never reported.

Adapalene plus BPO

Bettoli et al. [12] conducted a non-randomized intervention study treating 69 responders (defined as complete clearance after treatment with oral isotretinoin ≤ 0.2 mg/kg; duration specified as 'until clear') with adapalene 0.1%/BPO 2.5% fixed combination q.d. The only reported outcome was relapse defined as the re-occurrence of acne severity grade ≥ 0.5 (10 papules and pustules and 10 comedones), which was only experienced by 2 patients.

Azelaic Acid

Gollnick et al. [13] treated patients with AA 20% who had been treated with AA 20% b.i.d. plus oral minocycline 50 mg b.i.d. in the initial 6-month study and who had then achieved responder status (defined as number of deep inflammatory lesions that decreased by $\geq 75\%$, and the improvement of treatment was rated by patients as 'very good'). The second original study arm received no maintenance treatment. After 12 weeks, the patients

in the AA group experienced an increase in median lesion count (NIL from 13 to 17; IL from 3 to 7) whereas the no-treatment group saw almost no change (NIL from 8 to 7, IL remained 2). With regard to the global assessment of the patient's clinical appearance, in the AA group 38.5% of participants were classified as showing marked deterioration and 15.4% as experiencing slight deterioration whereas in the no-treatment group 4 and 46.2% of participants were classified accordingly. Note that only a fraction of patients per group was evaluated.

Isotretinoin

Meigel et al. [14] evaluated isotretinoin 0.2 mg/kg body weight or no treatment in patients who had achieved at least a two-thirds reduction in lesions after 12 weeks of induction treatment with isotretinoin 0.2, 0.5 or 1 mg/kg. The percentage of patients maintaining a 75% improvement in pooled NIL and IL lesion count was 72.5% in the patient group that was switched from 0.5 to 0.2 mg/kg ($n = 52$), 91.6% in the 1 mg/kg switched to 'no-treatment' group ($n = 26$) and 85.4% in the 1 mg/kg switched to 0.2 mg/kg group ($n = 39$).¹

Safety

Drop-outs due to adverse events were rare (0–2 patients, reported in 6 studies). Tolerability was reported by all authors with mild but mostly no burning/stinging [13], erythema or dryness [6–9]. Further details are provided in table 2.

Risk of Bias

Evaluations of the studies based on the seven predetermined risk of bias criteria are provided in figure 4. The risk of *other sources of bias* was 'unclear' for all RCTs due to reasons such as authors associated with sponsor [8] or different/inconsistent/missing baseline data [6, 7, 11]. Attrition and performance bias were rated to have a low risk of bias in most RCTs (methods used for randomization and blinding described). Only Zhang et al. [6] failed to describe the former and conducted an open-label trial. The risk of outcome data being biased cannot be precluded.

The non-randomized studies were evaluated to have a moderate to serious risk of bias. In all three studies the risk of baseline confounder and the risk of selective re-

¹ Note that only responders who received a lower dose (not the same dose) were considered for evaluation here because non-responders could also receive the same (or a higher) dose.

porting were serious due to some missing baseline [14] or outcome data [12], or unknowable modification of inclusion criteria [13].

Discussion

In our systematic review we found 8 studies assessing acne maintenance treatment. All studies were conducted after patients had gone through induction therapy and achieved a predefined improvement response. However, initial treatments before the maintenance phase varied strongly and are very likely to influence the outcomes of the maintenance periods. It would be desirable to have study designs, in which patient populations receive an identical initial treatment and then responders are randomized into different maintenance regimens. In addition to the limitations in study design, the definitions of responders varied between the included studies making comparisons difficult.

The available evidence for adapalene as a maintenance treatment is somewhat conflicting, depending on the assessed outcome. A benefit of maintenance treatment with adapalene/BPO was seen. For tazarotene and minocycline alone or in combination, no relevant differences during maintenance treatment were seen.

Due to the evaluation of different outcome measures and the divergent baseline situations in the non-randomized intervention studies, no overall conclusions could be drawn from these.

Limitations

Our search was limited to two online databases, and no hand searches were conducted. The effect sizes were only reported for RCTs because these tend to be inflated in non-randomized studies. We pooled data across 12 and 16 weeks, which neglects the duration of treatment.

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Conclusion

Pooled results somewhat support the use of topical treatments after the initial use of topical and systemic drugs.

The use of an appropriate maintenance study design (homogenous initial treatment phase study design, randomization into different maintenance regimens), standardized outcome measures and reporting of adverse events would be beneficial for the evaluation of different treatments.

Statement of Ethics

This is a systematic review, hence an IRB application was not required.

Disclosure Statement

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