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Acne Relapses and Maintenance Therapy: an Update on Definition and Prevention

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ABSTRACT

Acne vulgaris is a common chronic skin disease involving blockage and/or inflammation of pilosebaceous units. Acne can present as non-inflammatory lesions, inflammatory lesions, or a mixture of both, affecting mostly the face but also the back and chest. Variable rates of relapse after oral isotretinoin treatment have been published. This could be explained by different reasons; one of them is the lack of consensus about the definition of acne relapse after treatment. The objective of this review is to summarize all the different definitions of acne relapse proposed in the literature, in order to find a more reproducible and consistent characterization. This may become a useful tool that allows to compare the results obtained in future studies performed on acne relapses. As acne vulgaris is a dynamic entity that is notoriously difficult to assess over time, quantitative scales would be more indicated to evaluate its severity. In addition, the relapses after treatment are in correlation with the maintenance treatment phase. In this review, we also discuss the concepts of acute and maintenance phase of acne treatment. As the maintenance phase of treatment is a more recent concept, we consider necessary to review the features of this phase such as implantation time, treatment type, duration and efficacy. More studies, with a standardized relapse definition, are needed in order to determine efficacy rates and optimal duration of this phase. In conclusion, this review aims to highlight the need for a valid and reliable definition of acne relapse, especially for its use in research, but also highly valuable in daily clinical practice.

Keywords: Acne; relapses; maintenance phase; acute phase; recurrences; oral isotretinoin

ABBREVIATIONS

AP: Acute Phase; BPO: Benzoyl Peroxide Gel; IL: Inflammatory Lesions; Investigator Global Assessment (IGA) index; ISGA: Investigator´s Static Global Assessment; MP: Maintenance Phase; NA: Not Available; NIL: Non Inflammatory Lesions; OI: Oral isotretinoin; SGA: Subject´s Global Assessment

BACKGROUND

Acne vulgaris is an inflammatory, chronic relapsing disease of the pilosebaceous unit. It is characterized by long duration, with flares and remission periods and a high frequency of recurrences even after having received apparently satisfactory treatments [1]. Acne can be considered as an immune-mediated chronic inflammatory skin disease, as the innate immune response of these patients is not able to control *P. acnes*. It is followed by a Th1-mediated adaptive immune response that becomes self-maintaining independently from the pathogen [2].

As it mainly affects the facial region, the patient who relapses after being treated, suffers from a negative psychological impact, especially if the treatment was by oral route and for a long period, because the expectations then are usually very high.

There are many options available for the acne management, both topical and systemic treatments. As acne etiology has a multifactorial origin, the most common strategy involves the combination of different and complementary mechanisms of action [3]. The S3-guidelines, as well as expert's consensus statements, may be helpful during the election of treatment for a given patient [4-7].

Treatment choice is determined by acne type and grade, prior treatments, individual patient preferences as well as its impact on patient's quality of life and individual characteristics [4-7].

Different treatments, with a variable grade of recommendation are used for the management and treatment of acne. Topical therapies such as benzoyl peroxide; topical antibiotics (eg, clindamycin and erythromycin); combination of topical antibiotics and benzoyl peroxide; topical retinoids (eg, tretinoin, adapalene, and tazarotene); combination of topical retinoids and benzoyl peroxide/topical antibiotic; azelaic acid or dapsone have strength of recommendation (A). Oral antibiotics (tetracyclines, macrolides) and combined oral contraceptives have a high grade of recommendation (A) [6]. Topical salicylic acid has strength of recommendation (B). Chemical peelings (glycolic acid) also have a (B) grade of recommendation, as well as the complementary therapies, such as skin cleansers [6]. Oral Isotretinoin (OI) is one of the most effective drugs in acne treatment, acting on the four-pathogenesis cornerstones: hyperproliferation of follicular keratinocytes, hyperactivity of sebocytes, *Propionibacterium acnes* colonization and inflammation [8]. The drug produces a rapid and significant inhibition of the sebaceous gland activity within 2 to 4 weeks after therapy onset. The *P. acnes* population is also decreased during isotretinoin treatment, which may be due to a decrease in the intrafollicular lipids necessary for organism growth. OI also exerts anti-inflammatory activity as well as a regulatory effect on the pattern of follicular keratinization [8].

OI is indicated for severe acne unresponsive to other therapies. In the clinical practice, the prescription of oral isotretinoin has increased in patients with less severe disease or that have not responded successfully to conventional therapy [4]. It is reported to be also prescribed as a first-line treatment in mild acne when it is causing a devastating impact on patient´s quality of life [9,10]. In addition, despite the standard recommended dose has been set in 0,5-1 mg/ Kg/ day up to a total cumulative dose of 120-150 mg/ Kg, the current trend is to use lower doses of isotretinoin for a longer period of time[10]. Relapse rates after OI has been reported to vary from 5% to 65% [11]. The maintenance phase of treatment could decrease the relapse percentage[12]. The aim of the review is to summarize the different modalities of definition of relapses and maintenance therapy reported in the literature and describe a personal view of the authors on these matters.

PHASES OF TREATMENT: ACUTE AND MAINTENANCE

According to published studies, two different phases in the approach of acne patients exist. However, there is still no consensus on the exact definition of both treatment phases.

Acute phase (AP)

Several published studies consider the AP of treatment as corresponding to the first three months regardless of the modality, either topical or oral antibiotic [3,13,14]. In those patients treated with OI, the AP of treatment usually lasts for 6 to 9 months [15]. Through the oral and/or topical treatment of the AP, the response may be either complete disappearance or partial improvement of active lesions in comparison with baseline [16]. Current guidelines recommend OI as a first line treatment in severe papulopustular/ nodular and conglobate acne. Besides, some authors consider OI

appropiated for the management of moderate acne that is treatment-resistant or in those cases that generate physical scarring or psychosocial distress [6].

Maintenance phase (MP)

European guidelines include maintenance therapy supported by scarce evidence, according to evidence based medicine [12,13,16-18], but do not indicate if maintenance therapy should begin only after complete clearance of acne or if a partial improvement may be considered acceptable for starting a maintenance treatment [4]. However, different publications assess the benefit of a maintenance phase [12,19]. A standard definition of maintenance is still lacking, but the concept includes the use of appropriate therapeutic agents to ensure that acne remains in remission when the acute phase was satisfactorily finished.

The MP is defined in some studies as the approach after the first three months (in non-OI treated patients) and after six or nine months (in OI treated patients) [12,15,16,20-23]. Therefore, the duration of the MP is variable (3-9 months). Factors such as efficacy, tolerability and patient adherence should be taken into account when considering the duration of this phase. An effective agent should act, at least, on two of the acne pathogenic mechanisms and be able to be used over an extended period. Therefore, a topical retinoid represent an excellent choice during the maintenance therapy [15,20]. Treatments recommended for the maintenance phase as first-line include topical retinoids, such as adapalene 0.1% or tazarotene 0.1% with azelaic acid 15% or 20% as an alternative. Topical or systemic antibiotics are not recommended as maintenance therapy [24].

RELAPSES

Relapses definition

Unfortunately, there is no agreement in the definition of "recurrence" or "relapse" across the different studies, complicating the comparison of conclusions between studies. Usually, in dermatology, the term "relapse" refers to the appearance of new skin lesions after apparent healing. Nevertheless, this definition can be unclear and vague, because in some cases, a significant improvement of the disease is achieved without reaching the total disappearance of the lesions and, when the lesions arise again, it is interpreted as relapse [25].

Scales of acne severity index

The existence of several scales measuring acne severity [26-35] generates further complications in the consensus about the "relapse" term. A consensus on its definition would help when comparing the results of different acne relapse studies. In all of them, there may be a significant inter-observer variability, being more homogeneous with trained observers. The most used scales are those grading and counting the acne lesions [26-27]. The iconography provides a register of the patient's evolution throughout the entire course of the therapy and allows a bi-dimensional measurement. However, following this method makes more difficult to observe small or non-inflammatory lesions. The scrutiny of these lesions requires well-trained professionals and the need to standardize the features of the clinical pictures (light, distance, etc). This assessment is included in some of the most widely used severity acne grading scales such as the Modified Scale of Leeds.

Given the variability of acne treatments available and the existence of different measures for assessing its severity, we intend to propose the use of the same acne severity index scales to reach a consensus on the concept of "maintenance therapy" and "relapse" definition.

Relapses Incidence and risk factors for relapses after isotretinoin treatment

The association between isotretinoin dose and relapses has not yet been stablished yet as contradictory results were found. Layton mentioned that a total dose inferior to 120 mg/ kg was a prognosis factor for relapse [36]. However, recent studies suggest that isotretinoin dose would not be related to relapse rates [37-39]. Coloe, et al. [40] showed that patients who received a higher cumulative dose were less likely to require a second course of treatment, although a cumulative dose of isotretinoin did not significantly impact acne relapse. The treatment indication regarding dose and duration could be variable and subjective. In our clinical experience, patients affected with moderate acne and treated with OI achieve complete remission at even much lower cumulative doses than those recommended for severe forms (≥ 120 mg/kg) and our opinion is in accordance with the more recent studies that found that lower doses were not necessarily related to relapse [37-39].

There are some studies reporting the incidence of acne relapse after stopping OI, some of them with or without maintenance therapy. The relapse rate ranges between 9 to 92%[25]. Unfortunately, the studies are based on different designs, the definition of relapse is either lacking or different and the number of patients enrolled varies greatly (ranging between 52 and 17,351). The follow-up period also varies, from 1 to more than 5 years (Table 1).

To date, regarding the studies published about post-isotretinoin relapses, the publication of Azoulay, et al. [11] presents the largest number of patients enrolled (17,351 patients), and showed that 41% (7,100 patients) had relapses, defined by those patients who required either a second isotretinoin treatment or other anti-acne medication. It is important to stand out that more than half of the patients who relapse (4,100 patients) require a second course of OI (26%) (Table 1) [41]. Table 2 shows a list of factors associated with relapses.

The relapses after treatment during maintenance therapy and without maintenance treatment

We will analyze the relapses incidence after active treatment with OI or with topical and/ or oral therapy, with or without maintenance

Table 1: Percentages of relapses after isotretinoin treatment [25].

Authors	Nº Patients	Total Dose Oral isotretinoin	% Relapses
White GM, et al. [47]	179	> 100 mg / Kg - < 100 mg/ Kg	61% - 92%
Quereux G [41]	52	108-180 mg/ Kg	52%
Al-Mutairi N, et al.	117	0,5 – 1 mg/ Kg/ day for 6-28 weeks	49%
Coloe J, et al. [40]	102	216 – 268 mg/ Kg	45%
Lehucher-Ceyrac D et al	237	113-148 mg/ Kg	14%
Azoulay L, et al. [11]	17.351	> 2.450 mg	41%
Layton AM, et al. [36]	88	35-50 mg/ Kg	30%-39%
Liu A, et al. [49]	405	>150 mg/ Kg	23%
Stainforth JM, et al. [46]	299	> 0.5 mg/ Kg/day vs < 0.1 mg/ Kg/ day	17% - 23%
Harms M, et al. [44]	86	233 mg/ Kg	15%
Borghi A, et al. [12]	150	81 mg/ Kg	9%

therapy, in order to stablish the hypothetical relation between maintenance treatment and relapse rate.

Summary of the studies published about relapses after OI without maintenance therapy

The studies showed at Table 3 reflect that after OI without maintenance treatment, there are more and earlier relapses in those patients who had received lower doses and shorter time of treatment. Most authors define relapses after OI as acne presence demanding an under-prescription medication after a course of OI. Percentages of relapses have a great variability between 15% to 92% [42-52].

Table 2: Predictor factors for relapses after oral isotretinoin treatment.

Factors associated with relapses
· Male sex [25]
· Under 16 years old [25]
· Living in urban area [25]
· Cumulative doses of Isotretinoin: less than 2.450 mg [25]
· Isotretinoin time duration treatment: less than 121 days [25]
· Seborrhoea after treatment [25]
· High number of inflammatory lesions [41]
· Familiar history of acne [41]
· Trunk acne lesions [41]
· Smoking [41]
· Older age (women over 25) [11]
· Polycist ovarian syndrome [11]
· Absence of maintenance treatment with topical retinoids [40]

Summary of the studies published about relapses during the maintenance phase after receiving OI

Table 4 summarizes the studies of relapses during the maintenance phase after OI treatment [12,37,53,54,56,57]. Some authors of this paper tested the efficacy of adapalene 0.1% cream as a maintenance therapy after acne remission obtained with an OI course in 2 open-label prospective non-randomized studies. In the first study, 74 patients affected with moderate to severe acne were treated with adapalene 0.1% cream in a 12-month maintenance therapy and then followed up for a further 6 months without treatment. In the second study, 139 patients affected with mild to moderate acne were treated with OI until complete remission. Then the patients underwent a 12-month maintenance therapy with adapalene 0.1% cream. In both studies, relapse has been defined as the occurrence of acne with a severity grade ≥ 0.5 as per Leeds grading scale and/or requiring systemic treatment. Rates of acne recurrence observed were 6.7% and 9.35%, respectively [37,53]. This author also published a study with 68 patients who remained in the maintenance phase during one year with daily application of fixed-dose adapalene 0.1%-benzoyl peroxide gel (BPO) 2.5% gel. 2.94% of patients experienced a protocol-defined relapse [54].

Treatment failures with isotretinoin in female patients are frequently related to endocrinological dysfunctions, eg: polycystic ovary syndrome (PCOS). Hormonal interventions are prescribed for female patients with polycystic ovary syndrome and acne, regardless of serum levels of androgens. Oral contraceptive pill therapy is the first-line therapy for hirsutism and acne in women with PCOS. The estrogenic component suppresses luteinizing hormone and ovarian androgen production, enhances sexual hormone binding globulin (SHBG) production in the liver, thus reducing free testosterone. The least androgenic progestins (norgestimate and desogestrel) are

Table 3: Relapses after OI without maintenance therapy.

Publishing	#	Mg/Kg/day	Follow-up	Recurrence Definition	Results
Jones DH, et al. [38]	76	0.1 mg/ kg 0.5 mg/ kg 1.0 mg/ kg	16 weeks treatment 16-week follow-up	Not available	1.0 mg/ kg dose had more treatment
Strauss JS, et al. [42]	150	0.1 mg/ kg 0.5 mg/ kg 1.0 mg/ kg	20 weeks treatment 8- to 12-week follow up Patient questionnaire at 12–18 months	Not available	42% patients who received 0.1mg/kg/d required other course of treatment 20% patients who received 0.5mg/kg/d required other course of treatment **10%** patients who received 1.0mg/kg/d required other course of treatment
Wokalek H, et al. [43]	176	0.1 mg/ kg 0.5 mg/ kg 1.0 mg/ kg	12 weeks treatment 17-month follow up	Not available	First relapse in 1mg/kg/d group occurred 6 months after end of therapy All patients were in remission at 5 months 6 out of 26 patients had to restart acne treatment First relapse in 0.5mg/kg/d group occurred after 5 months First relapse in 0.1mg/kg/d group occurred after 2 months
Harms M, et al. [44]	86	Until 233 mg/ Kg	6-47 months (mean follow-up duration of 14 months after receiving oral isotretioin).	Not available	**15%**

Cunliffe WJ, et al. [45]	250	0.5 mg/ kg 1.0 mg/ kg	4 months treatment 12- to 50-month follow up	Not available	Relapse rates: • 42% with 0.5mg/kg/d • **13%** with 1mg/kg/d Significant differences between both doses were observed.p<0.01
Layton AM, et al. [36]	88	0.5 mg/ kg 1.0 mg/ kg	16 weeks treatment 10-year follow up	Not available	**39%** relapsed and required oral antibiotics or further isotretinoin 82% patients who received <120mg/kg cumulative dose relapsed vs. 30% who were given a larger dose (P<0.01) Majority of patients relapsed within 3 years of isotretinoin therapy 78% patients relapsed within 18 months
Stainforth JM, et al. [46]	299	0.1 mg/ kg 0.5 mg/ kg 1.0 mg/ kg	16 weeks treatment 5-year follow up	Not available	69% patients taking 0.1mg/kg/d isotretinoin who were followed relapsed 88% patients requiring more than 2 courses of isotretinoin were treated with 0.1mg/kg/d or 0.5mg/kg/d isotretinoin Only 9.5% patients needing >2 courses of isotretinoin were treated with 1mg/kg/d
White GM, et al. [47]	179	Examined total cumulative dose	20 weeks treatment 3-year follow up	Defined by receiving an antiacne medication: Required topical therapy, oral antibiotics plus topical therapy or required OI	**34.6%** patients had no recurrence 8% patients receiving <90mg/kg isotretinoin had no recurrence 40–50% patients receiving >110mg/kg isotretinoin had no recurrence Chance of recurrence is 8.2 times for patients taking a total dose of <100mg/kg vs. patients taking a total dose of >100mg/ kg
Haryati I, et al. [48]	193	Examined total cumulative dose	10 years	Defined by receiving an antiacne medication: Required topical therapy, oral antibiotics plus topical therapy or required OI	**Within the patient with relapses:** **17.5%** required topical therapy **3.3%** required oral antibiotic plus topical therapy **19.6%** required a second course of isotretinoin Total percentage of relapses: Total dose taken and duration of treatment was 103.5mg/kg during 6.7 months for patients who required further therapy and 118.55mg/kg during 7.41 months for patients who were cured after one course
Quereux G, et al. [41]	52	initial dose 0.3 to 1 mg/ kg/ day. Adapted according to tolerability and clinical outcome. Total acumulative dosis >120 mg/ Kg Average dosis by day 0,36-0,1 mg/ Kg	2 years	Relapse was defined by an increase in the number of lesions after isotretinoin withdrawal, with a score of 2 or more for superficial infl ammatory lesions (more than 4 papules or pustules), with a score of 3 or more for retentional lesions (more than 9 open or closed comedones) or with the presence of 1 or more nodules, which represents a deterioration in acne sufficient to merit a treatment.	52% patients relapsed
Azoulay L, et al. [11]	17.351	>2.450 mg <2450 mg	Inclusion: 1984-2003 48 802 person-years of follow-up	Defined by receiving an antiacne medication	41% patients relapsed (lower relapse rates with higher doses and longer treatment period, 121 days more than the average). Most of the Second isotretinoin treatments were dispensed within the first 2 years after the end of the first treatment
Liu A, et al. [49]	405	Isotretinoin for at least 150 mg/ Kg	Within the first 2 years	Relapses severe enough for the patient request further medical management	23% patients relapsed
Coloe J, et al. [50]	102	Oral Isotretinoin for at least 4 months	Al least 1 year follow-up	Defined as acne requiring a prescription medication after a course of isotretinoin; ‘‘retrial’’ was defined as recurrent acne severe enough to need a second course of isotretinoin.	45% patients relapsed

Table 4: Relapses during topical maintenance phase after OI.

Author	N	Maintenance therapy	Relapse Definition	Relapses (%)
Borghi [37]	74	Adapalene 0,1% cream 12 months	> 0,5 Leeds and / or requiring systemic treatment	6,7% of patients relapsed
Bettoli [53]	139	Adapalene 0,1% cream 12 months	> 0,5 Leeds and/ or requirement systemic treatment	9,35% of patients relapsed
Bettoli [54]	68	Adapalene 0,1-BPO 2,5% 12 months	> 0,5 Leeds and or requiring systemic treatment	2,94% of patients relapsed
Bettoli [12]	40	Biretix® 12 months	> 0,5 Leeds and or requiring systemic treatment	15,38% of patient relapsed
Vender [56]	20	Tretinoin 0,04% gel, 24 weeks Vs vehicle	ISGA, SGA	Mean lesions number 38.7% lower after retinoid treatment vs vehicle treatment
Truchuelo [57]	32	Biretix® vs vehicle, 3 months	Counting of lesions	17% of patients relapsed after biretix treatment vs 43% after vehicle treatment.

most helpful therapeutically, whereas the most androgenic progestins (norgestrel and levonorgestrel) should be avoided. Isotretinoin is useful in the management of acne of PCOS. Recurrences rates after OI treatment in PCOS patients, have not been published yet. The physician must be aware that isotretinoin has no efficacy in the treatment of hirsutism or androgenic alopecia [55].

In another study, Vender compared maintenance treatment efficacy of 0.04% tretinoin gel (microspheres) versus vehicle for 24 weeks in 20 patients previously treated with oral isotretinoin. The mean number of lesions in the treated group at the end of the maintenance phase was a 38.7% lower than the vehicle group. In addition, the ISGA (Investigator´s Static Global Assessment) showed better results in the tretinoin group during the entire maintenance period. The SGA (Subject´s Global Assessment) which was well correlated with the ISGA, also scored better results in the treated arm [56].

Truchuelo et al conducted a proof of concept, prospective, randomized, double-blind and vehicle-controlled study with Biretix®, a cosmetic combination of two retinoids (hidroxy pinacolone retinoate and retinol in glycospheres), during the maintenance phase. The study was conducted in 30 patients treated with OI previously and who reached an average dose of isotretinoin of 68.34 mg/ kg. The retinoid combination was used on a split-face model, applying the active product to one side of the face and the vehicle to the other, once daily for 3 months. The mean of follow-up was 6 months since treatment discontinuation and is important to highlight that relapses were defined as the increase in the number of any sort of lesion (inflammatory or non-inflammatory) [57]. On the treated side, only 17% (5 out of 30) showed relapses or worsening of initial condition vs 43% (13 out of 30) on the vehicle side (p = 0,021). The improvement perceived by the researcher was significantly better on the treated side than the vehicle (p < 0,01). Tolerance was excellent in all patients. The tolerance of the MP treatment is the key factor of success in order to maintain patient's adherence to treatment.

Confirming this preliminary results, Bettoli et al developed a study including 40 patients who had been treated with OI in the acute phase. The treatment reached a total OI accumulated dose of 77 mg/Kg. During the MP, patients were treated with Biretix®. The recurrence rate was 15% after one year of treatment. The results support the improvement in recurrence rates achieved with topical retinoids [12]. The results observed in the four studies that had one year of maintenance therapy, showed a lower rate of relapses (15% or less) when the MP starts immediately after finishing the course with OI.

Summary of studies published about relapses during maintenance therapy after non-isotretinoin treatment

Table 5 summarizes the studies with maintenance regimen after non-OI treatment acute phase treatment. Topical adapalene is the most frequently used agent for the MP according to published studies.

The use of topical adapalene for 12 weeks after an OI course reduces significantly the recurrence rates [16]. Tazarotene and azelaic acid may achieve improvement on recurrences with a minor impact than adapalene [7]. As adherence to treatment is an important key point in long-term therapies, this new retinoids combination (hidroxypinacolone retinoate and retinol in glycospheres), with very good tolerability outcomes, represents a novel option in the maintenance therapy. As shown in table 5, different percentages of relapses have been reported, ranging between 5% to 25%. Adapalene is the most frequently used drug. It is our understanding that the maintenance phase after non- OI treatment, could be shorter than the suggested year of maintenance after OI treatment. Lower percentages of recurrences were achieved with 3 months of maintenance therapy after non-OI treatment.

OUR EXPERIENCE ABOUT RELAPSES AND MAINTENANCE THERAPY

We suggest to differentiate the concept of relapse based on whether the treatment was topical, oral antibiotics or a combination of both of them; or if it was the "gold standard" oral isotretinoin.

RELAPSES AFTER NON-OI TREATMENT

Some authors (as summarize tables 3 and 4) define the term relapse on a re-treatment need basis (either with topical treatment or with oral isotretinoin) after prior healing [41,11,47,49-51]. Bettoli [53,54] had previously defined acne recurrence as the increase of > 0.5 points in Leeds scale or the need of systemic treatment. Other authors define this term based on grading scales such as worsening by the Investigator Global Assessment (IGA) index [22] or worsening by Investigator´s Static Global Assessment (ISGA) or Subject Global Assessment (SGA) [56]. However, these definitions are ambiguous and subjective and do not allow to unify concepts, making difficult, if not impossible, to reach adequate conclusions between different studies. After a thorough review of the different methods to assess "acne relapses" in several studies published in Pubmed, to our knowledge, we believe that one precise and objective definition for relapse would be the inability to keep a percentage of improvement in the count of lesions of at least 50% of the percentage improvement obtained after the acute treatment phase. This definition has been

Table 5: Studies in which a maintenance treatment was scheduled after the therapy of the acute phase (non-OI treatment) of acne. The table relates the relapses or the increase in count lesion number [13-15,22,23,58-61].

Author	Nº patients	Treatment	Maintenance	Relapse definition	Percetage of relapses or total lesion reduction
Zhang, et al. [23]	241	Clindamycin solution 1% + adapalene gel 0,1% or clindamycin solution 1% alone, 12wk	Adapalene gel 0,1% 12 wk	Mean percentage increment in lesion count (Response according to 5 point scale, Severity according to modified international acne grading system)	
					41% reduction of total lesions with adapalene vs 91% increase in vehicle patients
Thielitz, et al. [58]	49	Adapalene 0,1% gel + BPO 2,5% gel, 8wk	Adapalene gel 0,1% vs vehicle 12 wk	ND	Adapalene daily or every other day Significantly control the comedone count reduction
Thieltz, et al. [59]	36	Adapalene 0,1% gel 12wk	Adapalene 0,1% vs Azelaic acid, 9 month vs no maintenance	If unable to maintain 50% improvement	
		Azelaic acid 12wk			27% relapses after adapalene treatment vs 47% relapses after azelaic treatment.
Thiboutot, et al. [15]	253	Doxycline 100 mg + adapalene 0,1% gel, 12wk	Adapalene gel 0,1% vs vehicle 12wk	If unable to maintain 50% improvement (response according to 6 point scale; severity according to ³15 IL o 15-100 NIL	
					25% relapses after adapalene treatment (75% mantained the response) vs 46% relapses after vehicle treamten (only 54% mantained the response)
Alirezai, et al. [14]	136	Lymecycline 300 mg + adapalene 0,1% gel, 12wk	Adapalene gel vs vehicle 0,1% 12 wk	If unable to maintain 50% improvement (response according to 7 point scale and severity ussing leeds revised acné grading system O'Brien)	
					15,3% relapses after adapalene treatment (only 84,7% maintenance success rate) vs 36,5% relapses after vehicle treatment (only 63.5% maintenance success rate)
Cassano, et al. [61]	419	Lymecycline 300 mg + adapalene 0,1% gel	Adapalene gel 0,1% 12 wk	NA	5% patients relapsed
Leyden, et al. [13]	110	Minocyline 200 mg + tazarotene 0,1% gel	Tazarotene 0,1% gel vs minocycline vs both, 12 wk	If unable to maintain ³ 70% improvement (response according to 7 point scale, severity according to 10–100 facial NIL, 25–60 facial IL, ≤ 2 nodular cystic lesions)	11% patients relapsed with tazarotene treatment vs 13% with minocyline.
					No statistical significance between tazarotene alone and its combination with oral minocycline.
Gollnick, et al. [60]	71	Minocycline 100 mg + azelaic acid 20% cream vs OI	Azelaic acid 20% cream for 36 weeks	Increase in median lesion count (response if number of deep inflammatory lesions decreased by ≥ 75%, and efficacy of treatment was rated by patients as 'very good'. Severity according to Leeds scale.	Increased slightly from 13 to 17 comedones & 3 to 7 papules and pustules vs slight reduction in previous OI 8 to 7 comedones and no changes in papulopustules.
Poulin, et al. [22]	243	Adapalene 0,1% - BPO 2,5% gel + doxycycline 100 mg or vehicle + doxycycline 100 mg doxycycline 100 mg	Adapalene 0,1%-BPO 2,5% gel vs vehicle for 24 weeks	If unable to maintain at least 50% of improvement after active phase. Severity according to Investigators Global Assessment 6 point scale.	21,1% patient relapsed with adapalene-BPO(78.9% maintenance success rate) 54,2 patients relapsed with vehicle (45.8% maintenance success rate)

used by different authors, although with different severity scales, and we propose to take it as the standard definition for further studies [3,13-15,21-23,59]. This is a quantitative evaluation, different from others only based on subjective criteria. We strongly believe that it is necessary to include an MP of adjustable duration according to the patient's needs. If the relapse shows up during the MP, it would be necessary to switch to another therapy of MP.

In our opinion, the maintenance treatment after receiving topical therapy should last at least three months; therefore, the evaluation of a hypothetical relapse should be made at least, after this period. As it has been shown, there are significant differences in the response during this period [22] and it has been observed that this improvement continues [61].

RELAPSE AFTER TREATMENT WITH ORAL ISOTRETINOIN

As most of the relapses occur within the first 18 months after OI discontinuation, a 2-year follow-up could be adequate for accurate detection of acne relapses.

Some authors define relapse as increment in ≥ 0,5 Leeds and/or requiring systemic treatment after acute treatment [53,54,56,57]. Other authors defined relapse as the need of any type of treatment (topical or systemic) after OI course. We believe that Leeds scale is the best one to evaluate the acne severity. However, to assess relapses after OI treatment, we believe it should be easier and more practical

just quantify the number of lesions and compare it with the number at the end of the acute phase of treatment. In the case of OI, we propose to consider a relapse after OI if the patient is unable to maintain at least the 80% of the improvement achieved after the acute phase. To our practical experience, the concept of relapse defined as "unable to maintain the 50% of improvement after active treatment" would not be sensitive enough in patients who performed OI treatment. These patients of the achieve a complete response and the reappearance of a few new lesions is a source of emotional stress may require a new treatment. We also believe that relapse definition after OI, cannot be made only based on the need of new treatment either topical or systemic, as this need is a subjective concept which may vary between dermatologists and patients point of view. Regardless of whether the increase is a few or many lesions, as there is an important psychological impact in these patients, the new treatment (topical or oral) should be indicated. These reasons exposed above reinforce why the MP should be always implemented after an OI course.

This definition is also a claim to the standard application of a maintenance phase immediately after stopping the treatment with oral isotretinoin. The duration of this MP needs to be further elucidated with more clinical trials.

Within this context, the MP should be introduced after the discontinuation of OI and be maintained at least for one year [50]. Since there are a new retinoid combination (Biretix®) with minimal side effects, high tolerance and therefore high compliance by the patient, this maintenance therapy may be adequate for any patient who has completed a course with OI. Certainly, it would be strongly recommended in patients considered at high risk of relapse after OI [12,57].

We believe that the concept of relapse is directly correlated with maintenance therapy as we reported in the literature. If maintenance therapy after AP treatment is stablished in regular practice, the possibilities to relapse would be definitely lower.

CONCLUSIONS

The concept of acne relapse is in close relationship with MP. An MP with a topical and well-tolerated retinoid that allows patient's adherence would decrease the recurrence rates after active acne treatment.

As it is essential to standardize the definition of severity of acne as well as the response and relapse concept to be able to design comparable studies, we propose the Leeds Revised Acne Grading System O'Brien as the quantitative scale of election for classify the severity grade of acne. For determining the presence of recurrences we propose to use a quantitative scale instead. We claim the need to differentiate between those patients treated with OI during the AP, where relapse would be considered if unable to maintain at least 80% of the improvement achieve after the active treatment, from those who received non-OI treatment, where relapse would be considered if the patient is unable to maintain 50% of improvement achieved after the acute phase.

DECLARATIONS

Competing interests

M.T. Truchuelo: declares to be a dermatologist with occasionally works as is the scientific advisor to Industrial Farmaceutica Cantabria (IFC).

M. Vitale: declares to be a dermatologist MD Ph.D working for the Medical Department of Industrial Farmaceutica Cantabria (IFC).

V. Bettoli and JL. Lopez-Estebaranz declares that they have no competing interests.

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Authors' contribution

MT participated in the conception and design process. Also reviewed and analyzed the articles published in the literature and extracted data. Interpreted all the data.

MV participated in the conception and design process. Also reviewed and analyzed the articles published in the literature and extracted data. Interpreted all the data.

VB: Interpreted all the data and revised the manuscript critically.

JE: Interpreted all the data and revised the manuscript critically.

All authors read and approved the final manuscript.

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