Current guidelines in the treatment of acne vulgaris: from the approach in the acute phase to maintaining the clinical benefits

Diretrizes modernas no tratamento da acne vulgar: da abordagem inicial à manutenção dos benefícios clínicos

ABSTRACT

Acne is a multifactorial disease encountered on a daily basis by general medical practitioners and, especially, dermatologists. It has been a constant focus of studies that increasingly unveil details of its physiopathology and help refine treatments in order to address the majority – if not all – pathogenic factors. This article's objective is to draw attention to the therapeutic associations and combinations in acne management, highlighting its chronic disease character, typified by recurrence, and the requirement for continued treatment that is not only effective but also safe.

Keywords: acne vulgaris; acne vulgaris/pathophysiology; drug resistance, bacterial.

RESUMO

Afecção multifatorial presente no cotidiano dos consultórios médicos de modo geral, em especial nos dermatológicos, a acne tem sido foco constante de estudos que desvendam cada vez mais detalhes de sua fisiopatologia e possibilitam refinamento terapêutico de modo a atingir, senão todos, a maioria de seus fatores patogênicos. Este artigo visa destacar as associações e combinações terapêuticas no manejo da acne, ressaltando-a como doença crônica que cursa com recorrências e necessita de manutenção terapêutica não só eficaz, mas, principalmente, segura.

Palavras-chave: *acne vulgar; acne vulgar/fisiopatologia; farmacorresistência bacteriana.*

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INTRODUCTION

As established by the Global Alliance to Improve Outcomes in Acne (GAIOA) members in 2009, acne must be considered a chronic disorder and not an affliction limited to adolescence.[1-3] It presents a pattern of recurrence and a prolonged course; manifests with acute eruption or insidious beginning; and affects patients psychologically and socially – features typical of chronic disorders.[4] There is also abundant evidence that acne persists into adulthood in about 50% of individuals.[5]

Acne is currently the focus of studies that have been enhancing the understanding of its physiopathology and treatment. Combined therapy has been recommended as the first choice in acne treatment.[6] The treatment should be early and aggressive in order to reduce the physical and emotional impacts on the patient.[7] In order to minimize the risk of recurrence and obtain favorable results, therapeutic maintenance is necessary.[8-10]

PHYSIOPATHOLOGY

There are four factors involved in the pathogenesis of acne: hypersecretion of the sebaceous gland, alteration in the keratinization process, colonization by *Propionibacterium* acnes (*P acnes*), and the liberation of inflammatory mediators in the skin. [10, 11]

Sebaceous hypersecretion

Acne attacks primarily the face, anterior thorax, and dorsum − areas with great concentrations of pilosebaceous follicles. [12-15] Around the age of 7, the sebaceous glands and the follicular keratinocytes are stimulated by androgenic hormones, resulting in higher sebaceous production and follicular hyperkeratosis; microcomedones form at this time and, later on, inflammatory lesions. [16,17]

The sebaceous cells and the keratinocytes possess enzymes as 5α-reductase, $3,\beta$ and $17,\beta$ hydroxysteroid dehydrogenase, which are capable of metabolizing the androgens. [18-22]

With time, the sebaceous cells differentiate and break up, liberating lipids in the sebaceous ducts and follicles. [12] In general, sebaceous production depends on the circulating androgens and on the response of the pilosebaceous unit.

The sebaceous lipids are regulated in part by receptors activated by peroxisome proliferators and by a transcription factor denominated SREBP (Sterol Responsive Element Binding Protein). [23,24] The sebaceous glands in turn perform independent endocrinal functions in the skin, with an important role in cutaneous hormonal maturation. [25,26] They constitute an organ with an neuroendocrinous-inflammatory function that coordinates and executes the local response to stress. [6]

Follicular keratinization disorder

Comedogenesis is caused by the abnormal desquamation of corneocytes (keratinized cells) that accumulate in the sebaceous follicles, which results in the formation of a microcomedone, a microscopic lesion. [27] Over time, the follicle accumulates lipids, bacteria and cellular fragments; it increases in size and develops into a comedo, a clinically detectable lesion that can be inflammatory (open comedo) − caused by bacterial proliferation and inflammatory mediators − or noninflammatory (closed comedo). [28,29]

This process, called keratinization, may be related to decrease of linoleic acid in sebum, [30,31] the proliferation of type 1 5α-reductase in the infundibulum, and abnormal lipidic inclusions linked to defects in corneocytic differentiation. [29,32-34] The changes in the composition of the sebum can irritate the infundibular keratinocytes, liberating interleukin-1 (IL-1), an inflammatory mediator also related to comedogenesis. [35,36]

Bacterial proliferation

P acnes, an anaerobic gram-positive bacterium, proliferates in the follicular duct. It

hydrolyzes the sebum's triglycerides through the esterases, which results in free fatty acids that irritate the follicular wall

and induce keratinization. [37]

The innate immune response is the first line of defense against infectious illnesses, [38] and *P acnes* takes part in the activation of that response. [39] Components of *P acnes* can activate the TLR (toll like receptor-2), [70,11] a mammalian homologous to the Drosophila fly protein. [41] There are 11 types of TLR; [42] *P acnes* possesses a soluble factor that, in the presence of CD14 lymphocytes, is able to activate TLR (mainly TLR-2 and –4), [11] and induce the synthesis of local pro-inflammatory factors, such as the α-tumor necrosis factor (TNFα), interleukin 1β, prostaglandins, leukotrienes, and IL-8. [43-45]

The reduction of *P acnes* seems to correlate with the clinical improvement of acne, probably due to the reduction of inflammatory mediators induced by the microorganism itself. [12,46,47]

Inflammation

Inflammatory lesions, including papules, pustules or nodules, may develop from one type into another and even scars. [47] Inflammatory lesions begin with the formation of a papule; a microcomedone is present beforehand in 80% of such lesions. CD4 Lymphocytes and neutrophils invade the follicle, and the rupture of the duct causes a discharge of lipids, corneocytes and bacteria into the dermis. [47] There is liberation of cytokines and neuroinflammatory mediators, since the sebocytes seem to express neuropeptides − such as Substance P − which in turn affects the size of the sebaceous gland, as well as its sebaceous production. With that, it contributes to the disorder in the differentiation, proliferation, and synthesis of lipids. [48]

It was recently described that the immunological alterations and inflammatory responses precede the hyperproliferation of keratinocytes in the pathogenesis of acne, a phenomenon similar to the type-IV immune response of delayed hypersensitivity. [49]

Excess sebaceous production and the alteration of follicular integrity are related to a deficiency of linoleic acid. [11, 31] In response to this deficiency, an increase in 1-α interleukin occurs, [49] contributing to the inflammation. Moreover, CD4 lymphocytes and macrophages are involved in the production of cytokines, which activate local endothelial cells and attract inflammatory markers such as E-selectin, VCAM-1, ICAM-1 and HLA-DR in the vasculature surrounding the follicles. [49]

Methyl metalloproteinases (MMPs) are endopeptidases produced by diverse types of cells, including keratinocytes, that are capable of destroying the components of the extracellular matrix. [50,51] By causing the rupture of the pilosebaceous follicle, MMPs exacerbate the spread of the inflammation. [52]

TREATMENT

The latest normative guidelines in the approach to acne vulgaris incorporate GAIOA's recommendations (2009). [7] These guidelines help clarify treatment options for acne patients and verify whether the chosen approach is aligned that of other

dermatologists around the world – especially concerning the clinical efficacy and therapeutic safety of prescribed medications. It is with this in mind that we have developed this article.

1 – Classical treatments
Topical Retinoids

There is a consensus that topical retinoids (isolated or in combination) are the first line of treatment of light to moderate acne, and are often prescribed to minimize the use of antibiotics.[53] In general, topical retinoids control the development of microcomedones, reduce blackheads and existing inflammatory lesions, and minimize the formation of new lesions.[55]

Retinoids reduce the desquamation of the epithelial follicles [54,55] and modulate the immune response to produce an anti–inflammatory effect.[6,56] They inhibit the formation of microcomedones and alter the follicle, facilitating the penetration of compounds such as benzoyl peroxide (BPO) and topical antibiotics.[30,57-59]

Topical retinoids, such as adapalene and tretinoin, reduce the free fatty acids produced by the triglycerides' metabolization of the *P acnes*' lipase enzyme in the microcomedone.

However, the microcomedones re-appear after the treatment stops. Therefore, topical retinoids should be used in maintenance treatment to prevent recurrence.[55]

Topical bactericides and bacteriostatics

Over the years, effective topical bacteriostatic or bactericidal products – including BPO, erythromycin, clindamycin and azelaic acid – have been introduced in the treatment of acne vulgaris.[60]

BPO, a bactericidal product, was introduced in the treatment of acne in 1934, and is considered the benchmark in topical therapy. Anaerobic bacteria are reduced by oxidative mechanisms. Topical formulations are available in 2.5, 5, 10, and 20% concentrations. Its effect, as well as the irritative effects, depends on the dosage. [61]

Azelaic acid also has bactericidal effects, and is not an antibiotic. [61,62] It is a saturated dicarboxylic acid that, as an antimicrobial agent, helps normalize follicular ostium keratinization. [63,65-67] Systemic effects are uncommon, and it is safe to use during pregnancy and breastfeeding. [61]

Topical antibiotics, such as clindamycin and erythromycin, are available in the form of solutions, lotions, gels and also combined with BPO. They reduce the population of *P acnes* in the pilosebaceous duct. While topical antibiotics can cause local irritation, other adverse effects are less significant than those caused by systemic antibiotics.[68,69] Although topical application of tetracycline is an option, a 1990 scientific review suggests that it is ineffective in treating acne.[61]

Systemic antibiotic therapy

At their first meeting in 2003, GAIOA established the following guidelines for systemic antibiotic therapy for acne:[6]

Posology of oral antibiotics used in acne treatment

First line:	Alternatives:
Tetracycline 500 mg, 2x/day	Erythromycin 500 mg, 2x/day
Doxycycline 50-100 mg, 2x/day	Trimethoprim 300 mg, 2x/day
Lymecycline 150-300 mg, 1x/day	Sulfamethoxazole-Trimethoprim 800/160 mg
Minocycline 50-100 mg, 2x/day	

The increasing antimicrobial resistance to erythromycin and other macrolides limits their use in cases where tetracyclines are contraindicated or not tolerated, such as during pregnancy or breastfeeding and in children.[4,27-30] In such cases, sulfamethoxazole-trimethoprim, a third line agent, can be used.[22]

Second-generation tetracyclines, such as minocycline, doxycycline and lymecycline, produce a quicker clinical response compared to their first–generation counterparts. When the emergence of new inflammatory lesions decreases or ceases, the dosage should be reduced gradually.[34] The use of topical retinoids is necessary to prevent a recurrence. Oral antibiotics are usually well tolerated.[4,23]

Macrolides and tetracyclines can cause gastrointestinal intolerance. [4,33] Tetracyclines might also inhibit axial growth in fetuses and cause discoloration of the dental enamel in children under 10 years.33 Minocycline might cause discoloration of scars and photoexposed areas, in addition to benign intracranial hypertension and drug–induced lupus.[22,35-37] In women, it can also cause candidiasis during the active period of the antibiotic.33 Lymecycline has been shown to be as effective as minocycline, and has a better safety profile.[38]

Any systemic antibiotic alternative to that recommended and validated by the GAIOA does not necessarily take either efficacy or safety into consideration in the approach to treating acne vulgaris. Nevertheless, in Brazil an audacious (yet unadvised) is in rampant growth: pulse therapy with azithromycin – the most popular example of the macrolides class.

The choice of antibiotic implies not only an understanding of the pathogen and its susceptibility, but also the antimicrobial's spectrum and pharmacokinetic properties, aiming at avoiding ecological effects such as bacterial selection.[70] Macrolides are bacteriostatic antibiotics that have shown to be effective against several skin infections. They inhibit the microorganism's protein synthesis.[71]

For the treatment of acne vulgaris, azithromycin pulse therapy is administered in doses of 500 mg/day for 3 days, in a total of 3 intermittent cycles, with 7-day intervals. This therapy has demonstrated good tolerability and effectiveness, [72,73] which has also encouraged patient adhesion to the treatment regime.[72] Many studies have been carried out to evaluate azithromycin's efficacy. It has been shown to be safe and effective in the treatment of acne vulgaris in adolescents and adults, in 3-weekly doses of 500 mg over 12 weeks [74] or 8 weeks, as shown in another study that assessed only adolescents.[75] Azithromycin (dose of 500 mg/day, for 4 days, in 4 cycles with 10-day intervals) was found to be as effective and well tolerated as minocycline (dose of 100 mg/day for 6 weeks).[76]

To some authors, the advantage in prescribing

azithromycin in the clinical treatment of acne is its easy adherence posology (single daily dose for 3 days). However, its plasma half–life is 68 hours (clarithromycin's, for instance, is only 5 to 7 hours). This characteristic means that azithromycin can persist in the plasma for at least 3 to 4 weeks after the end of treatment.

This persistence in subinhibitory concentration contributes to streptococcal resistance, which occurs more with azithromycin than with clarithromycin. There are also reports of its superiority in the resistance against *S. Aureus, Enterobacter spp* and *Klebsiella spp.*[70,77]

In general, the use of antibiotics is not innocuous. Macrolides, in turn, represent a risk for the patient of promoting bacterial resistance. There are several possible mechanisms that induce such resistance. One is the substance's active efflux by the bacterial plasma membrane, encoded by the gene *mef* ("macrolide efflux"). That mechanism presents low to moderate resistance to the macrolides, increasing its minimum inhibitory concentration. Another mechanism is linked to the *erm* (B) gene, which encodes methylase, altering the linking site of the antibiotic in the subunit 50S of the bacterial ribosome. [77] Azithromycin selects the microorganisms quantitatively soon after the therapy, while clarithromycin selects them qualitatively through the *erm* (B) gene. Both antibiotics possess high extracellular concentration in the breathing tissues such as the nasal and oral mucous membranes. The commensal flora, when exposed to those antimicrobials, can work as a resistance reservoir against potential pathogenic bacteria. The prolonged use of azithromycin increases the risk of the spread of resistant microorganisms in the community.[77]

A recent study conducted in Finland evaluated the regional resistance of *Streptococos pneumoniae* to the macrolides, comparing it to the local use of all macrolides combined and to the isolated use of azithromycin. The resistance to penicillin was also evaluated and compared with that caused by the consumption of penicillins in general, cephalosporins, all associated beta–lactams, and all the associated macrolides. [78]

The use of macrolides, including azithromycin, is correlated with the increase in resistance to macrolides, while the use of beta–lactams and cephalosporins is correlated to a small increase in the resistance of *S. pneumoniae* to penicillin. This data reinforces the argument against improper prescriptions of macrolides and cephalosporins. [78]

Hormone therapy and medicines to control peripheral insulin resistance Hormone therapy is a good option for women that want to use oral contraceptives or as an alternative to repetitive courses of isotretinoin. It can also be administered to women who present cases of serious seborrhoea and signs of hyperandrogenism, such as androgenetic alopecia, acne and hirsutism (i.e., Saha Syndrome – seborrhoea, acne, hirsutism and alopecia).[5] This condition can sometimes involve an insulin peripheral resistance, which must be treated with medicines almost always combined with hormonal contraceptives. [79]

We must always suspect endocrine disorders in women with acne that is resistant to conventional treatments. It often comes down to a physician's skills in looking for other complaints and examining the patient in a holistic way to confirm an endocrinologic diagnosis, not just focusing on acne lesions that prompt the patient's medical visit. This underscores the importance of the generalist education of the Dermatologist.

In this class of medicines we can find: 1) antiandrogens; 2) ovarian and adrenal hormone blockers; 3) non-hormonal controllers of the peripheral resistance to insulin; and, in the future, 4) inhibitors of the enzymes involved in androgenic metabolism in the skin.[79]

1) Antiandrogens

a) Cyproterone acetate: used for precocious and serious acne or suspicion of hypersensitivity of the sebocytes to peripheral androgens. It is a 17-α hydroxyprogesterone derivative (inhibits the central secretion of gonadotrophin and the activity of the 5-α reductase in the peripheral receptor). 80 The most popular commercial combination is the 17-α hydroxyprogesterone (2 mg) with ethinyl estradiol (35 mcg), which, in general, clears the acne in 12 to 24 cycles. The improvement of hirsutism occurs within 3 to 6 months of treatment.[79,80]

b) Spironolactone: its use can vary from 2 to 24 months, and can be combined with topical and/or systemic treatments, as well as with oral hormonal contraceptives. [79] The usual dose can vary from 100 to 200 mg/day. In the presence of an adverse event, however, the dose should be decreased (50 to 100 mg). 80 The majority of patients do not present adverse effects (57.7%); 17.5% present menstrual alterations; and 16.3% present alterations of the central nervous system, such as lethargy, fatigue, dizziness, and cephalea. 79 c) Others: due to their off-label use, for not being well established (finasteride) or for having been banned in dermatology (flutamide), they will not be discussed here.

2) Ovarian and adrenal hormone blockers

a) Oral hormonal contraceptives: inhibit the secretion of gonadotrophins, ovarian or adrenal androgens, in addition to stimulating the hepatic synthesis of sex hormone-binding globulin (SHBG), which reduces the plasmatic concentration of free testosterone.[80] Secondarily, it reduces the levels of IGF-1 and 5-α reductase. [79] The most popular and effective associations are: ethinyl estradiol (35 mg) with triphasic norgestimate (180 mg/215 mg/250 mg); and ethinyl estradiol (20 mg) with norethindrone (100 mg). Clinical improvement is observed within 3 to 6 months of continuous use. [79]

b) Gonadotrophin liberation agonists: infrequently used because they eliminate ovarian function, creating undesirable menopause symptoms. Possible medicines include buserelin, nafarelin or leuprolide.[6,79] Given the complexity of the patients' clinical follow up during the administration period of this class, its prescription and therapeutic oversight is performed by endocrinologists or gynecologists in the vast majority of cases.

c) Glucocorticoids: combined with oral hormonal

contraceptives. They inhibit the production of cortisol and powerful androgenic precursors. They are only suitable in the presence of congenital adrenal hyperplasia due to the deficiency of 11 or 21-hydroxylase. The most popular and safest option is prednisone, 2.5 to 5 mg at bedtime.[6,79]

3) Non-hormonal controllers of peripheral resistance to insulin

a) Metformin: an oral normoglycemiant, classified as an antidiabetic of the biguanides class.

In cases of peripheral resistance to insulin present in Polycystic Ovary Syndrome, it reduces the activity of the luteinizing hormone, inhibits the secretion of prolactin, stimulates ovulation, inhibits hepatic neoglycogenesis, inhibits the intestinal absorption of glucose, stimulates the peripheral sensibility to insulin and reduces low density lipoproteins/triglicerydes, in addition to facilitating weigh loss. Nevertheless, frequent gastrointestinal adverse events, such as diarrhoea, flatulence, nausea and vomiting are observed; these side effects are dosedependent and adaptable with continuous use. The usual dose varies from 1,500 to 2.550 mg/day.[79–81]

b) Glibenclamide: an oral hypoglicemiant, classified as an antidiabetic of the sulphonylureas class. It acts by stimulating the synthesis of insulin. This medication, unlike metformin, can cause classic symptoms of hypoglycemia; moreover, it can generate hematopoietic- and disulfiram-like reactions. Its usual dose is 2.5 to 5 mg/day (maximum 15 mg/day). [82]

Oral Retinoids

Created in 1955, isotretinoin, or 13-cis-retinoic acid, was first used in Europe in 1976, in 1980 in the United States, and in 1982 in Brazil.[60] Isotretinoin is an oral retinoid suitable for severe nodular acne or severe acne that does not respond to topical treatment.[83–84] It works by reducing the volume of sebaceous gland secretion, normalizing follicular keratinization and preventing the formation of new blackheads. With that, the number of *P acnes* is indirectly reduced.[5, 85]

The initial dose varies from 1 to 2 mg/kg/day, with the possibility of reduction after 45 to 60 days, with a minimum daily dose of 0.5 mg/kg/day. The minimum treatment duration is five months, depending on the daily dose and the patient's weight, with a minimum total dose of 120 mg/kg that could reach 150 mg/kg.[60,84]

The most common side effects are: labial dryness or cheilitis; drying of the nasal mucous membrane (which could cause nosebleeds); xerophthalmia; skin xerosis with desquamation and pruritus that can be more intense in atopic individuals; and minor alopecia. Other rarer reactions are cephalea, arthralgias, muscular pains (mainly in athletes), nervousness, insomnia, and a rise in cholesterol and triglycerides. [60]

Since it is a teratogenic medicine, it is important to exclude the risk of pregnancy before starting administration. The use of oral contraceptives should be maintained during the entire course of treatment and up to 30 days after the last dose.[39]

Regarding drug interactions, it is worth noting that vitamin A exacerbates the toxic effects of retinoids. In addition, its concomitant use with tetracycline can induce pseudotumor cerebri syndrome. [83]

Recurrence is common after isotretinoin therapy. Some respond to retreatment with conventional therapy, however the majority of the patients require a new isotretinoin cicle. [6]

The GAOIA intends to publish an additional article on the use of oral isotretinoin.[7]

Associations and therapeutic combinations: modern approaches to the treatment of acne vulgaris

Currently, the use of therapeutic agents with complementary mechanisms, such as the combination of topical retinoids and non-antibiotic antimicrobials (e.g., BPO), is considered the first line of treatment for acne. Its objective is to encompass multiple pathogenic factors, concomitantly treating inflammatory and non-inflammatory lesions.[6,69,85] The therapeutic combinations and associations are present in almost all grades and intensities of acne vulgaris, as demonstrated in Table 1. [7]

An additional aspect to be highlighted is the need to limit the frequency and duration of use for topical and/or systemic antibiotics, to avoid bacterial resistance, which worsens with the use of systemic antibiotics.[7]

When it is necessary to use topical antibiotics, it is recommended that they be combined with BPO, with preference given to the use of clindamycin as the associated antibiotic.[89,90] A 10-week, double-blind, randomized study evaluated the topical use of BPO 5% with clindamycin 1% in gel in patients with moderate to severe acne,, and found that the combined therapy was well tolerated and more effective than the isolated use of its components.[89]

A 16-week, double-blind, randomized study compared the use of clindamycin 1% combined with BPO 5% gel versus clindamycin 1% gel in monotherapy. There was a 1,600% increase in the resistance of *P acnes* during the use of isolated clindamycin,[90] demonstrating the importance of therapeutic associations in acne treatment.

According to the current directive, when it is necessary to use oral antibiotics for a prolonged period, it is recommended to use a non-antibiotic antimicrobial topical agent, such as BPO, due to its high bactericidal action, to reduce the development of bacterial resistance.[53,91- 93]

Over the years, it was noticed that the topical use of a systemic retinoid, adapalene, had a potentializing action on the clinical efficacy of antibiotic therapy – either topical or systemic.

Clinical studies showed that the topical use of adapalene, combined with topical clindamycin or systemic lymecycline, is more effective than the isolated use of these antibiotics.[6]

According to double-blind studies published in 2007 and 2009, the topical use of adapalene 0.1% combined with BPO 2.5% in a single product demonstrated superior results when compared to monotherapy or to the isolated use of the vehicle.[84,90] Adapalene, with its anti-comedogenic, comedolytic

Table 1 - Approach to acne treatment				
Light acne		**Moderate acne**		**Serious acne**
Comedogenic	**Papulopustulosa**	**Papulopustulosa**	**Nodular**	**Nodular/Conglobate**
Topical retinoid	Topical retinoid + topical antimicrobial	Topical retinoid + oral antibiotic +/- BPO	Topical retinoid + oral antibiotic + BPO	Oral isotretinoin
Alternatives: topical retinoid or azelaic acid or salicylic acid	Alternatives: Topical retinoid, antimicrobial + alternatives: topical retinoid or azelaic acid	Alternatives: oral antibiotic + alternatives: topical retinoid +/- BPO	Isotretinoin or alternatives: oral antibiotic + alternatives: topical retinoid +/- BPO /azelaic acid	Oral antibiotic in high dose + topical retinoid + BPO
—	—	Antiandrogens + topical retinoid/ azelaic acid +/- topical antimicrobial	Antiandrogens + topical retinoid +/- oral antibiotic +/- topical antimicrobial	Antiandrogens in high dose + topical retinoid +/- topical antimicrobial
Topical retinoid +/- topical antimicrobial		Topical retinoid +/- BPO		

n	1st choice	n	Alternatives for female patients
n	Alternatives	n	Maintenance treatment

Adapted from "New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne Group.[7]

and anti–inflammatory properties, when combined with BPO – which in turn is a potent bactericidal agent (more effective than topical antibiotics) – led to a reduction in inflammatory and non–inflammatory lesions in less than a week of use.[94] The anti–inflammatory synergy of adapalene and BPO resulted in: 1) the elimination of *P acnes* by BPO; and 2) the "downregulation" effect of adapalene on the TLR–2, used by *P acnes* to induce the production of inflammatory cytokines. Moreover, BPO penetration is facilitated by the retinoid.[94]

The combination of 0.1% adapalene with 2.5% BPO (both substances in their loweest effective doses) is tolerated well enough for daily applications.[95]

Triple combinations may prove to be a more effective topical therapy in the treatment of acne. Clinical reports point towards a possible benefit of using adapalene or tretinoin combined with BPO and clindamycin.[7]

The combination of adapalene with BPO and clindamycin has been evaluated. A multicentric study was conducted with 3 treatment groups: 1) clindamycin/BPO for 4 weeks followed by clindamycin/BPO and adapalene; 2) adapalene in monotherapy for 12 weeks; 3) clindamycin/BPO and adapalene for 12 weeks. Group 3 reported a better reduction in lesions.[96]

Tretinoin has also been studied in combination with BPO and clindamycin. In a controlled study, 3 treatment groups were compared: 1) clindamycin/BPO; 2) clindamycin/BPO and tretinoin 0.025%; 3) clindamycin/BPO with tretinoin 0.025% and clindamycin. In this study, the triple combination proved more effective in reducing inflammatory lesions (69%), followed by the first group (66%) and then the third group (52%). The

inflammatory lesions were reduced by the triple therapy (61%), followed by the clindamycin/BPO (57%) and then by tretinoin and clindamycin (50%). However those associations are still in the level III of evidence and are awaiting more studies regarding safety.[97]

Maintenance treatments

Acneic lesions tend to reappear over the years, especially when treatment is interrupted.[1,30,95] In this manner, maintaining the treatment is a way to avoid the reemergence of the lesions. For a long time, antibiotics were used for prolonged periods in patients with acne. However, that practice is not recommended due to its inducing microbial resistance.[91] In contrast to retinoids, antibiotics do not prevent the development of microcomedones – the precursors of acneic lesions.

International directives have indicated that topical retinoids are the medicine of choice for the therapeutic maintenance of acne vulgaris since 2003.6 Since topical retinoids prevent the development of new lesions and resolve existing lesions, they should be preferred as a monotherapy in the therapeutic maintenance of acne.[6]

Depending on the severity of the inflammation, other antimicrobial agents, such as BPO or a combination of BPO with antibiotics, can be combined with topical retinoids.[7]

Topical retinoids are available in several concentrations and formulations. The selection should be based on the patient's routine to guarantee a better adherence to the treatment.

Patients are also more likely to follow the treatment plan if they understand the gravity and clinical behavior of the

condition. Retinoids also attenuate post–inflammatory hyperpigmentation, which can be used as a strong argument to induce patient adherence.

CONCLUSIONS

There are a number of medicines available to control acne. Approaching acne as a chronic disorder, we emphasize the importance of maintenance therapy to avoid possible recurrences. Towards that end, the patient's adherence to the treatment is indispensable.

Investing in the physician–patient relationship may be very valuable in that sense. Explaining the disorder's behavior and adapting the administration of the medicines to the patient's routine may also favour the adhesion to the treatment.

Acne is a field of permanent research. Advances in the understanding of its physiopathology contribute to improvements in treatments, which comprise an increasing number of factors and provide patients with better results. ●

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