REVIEW

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Adjuvant therapies of acne: review of literatures

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ABSTRACT

Acne is a chronic inflammatory disorder affecting pilosebaceous unit with various clinical manifestation from comedone, papule, pustule, to nodule and cyst. Choice of treatment is based on acne severity. Prolong antibiotic use along with restriction of isotretinoin use in Indonesia can be a challenge in managing acne. A lot of treatment options from topical agent, systemic medication, comedone extraction, intralesional corticosteroid injection, chemical peeling, light and laser-based therapy, as well as diet modification can be used as an adjuvant to improve acne. Review of literatures was performed to present recent evidence toward the effectivity of adjuvant therapy as a part of acne management.

Keywords: acne, adjuvant, treatment, review.
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INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory disorder of pilosebaceous unit that is often discovered especially in the adult population. Clinical manifestations include comedone, papule, pustule, and nodule with various severities. AV is among the top three prevalent skin diseases. Although AV is common and mostly self-limited, AV often causes several complications, mostly pigmentation and scars, which further increase the risk of psychological disorders and decrease quality of life.[1]

Four main factors contribute to the pathogenesis of AV, which are follicular epidermal hyperproliferation, increased sebum production, colonization of *Propionibacterium acnes,* and impaired immune and inflammatory responses. In addition to genetic predisposition, hormonal factors, diet, and stress also play significant role in the development of AV. These four main factors of AV pathogenesis are targets for AV therapy.[1] In general, the choice of AV standard treatment is determined based on severity of AV. AV is classified into mild, moderate and severe based on the classification by Lehmann et al. in 2002 (Table 1).[2] Various guidelines for AV management are available in Europe, United States, as well as Southeast Asia. AV management guideline in Indonesia was developed by Indonesia Acne Expert Meeting. First-line treatment for mild AV includes retinoic acid and keratolytic, while azelaic acid is used for second-line treatment. Third-line treatment includes combination of retinoic acid and benzoyl peroxide (BP) or topical antibiotics. For moderate and severe AV, first-line treatment includes retinoic acid, BP or topical along with oral antibiotics. Isotretinoin and antiandrogen can be use as systemic alternatives for severe acne. Intralesional corticosteroid injection is considered for nodular lesion. Standard treatment from the first-line to third-line and alternatives are adjusted according to the clinical evaluation during 6 to 8 weeks.[3]

In addition to emerging antibiotic resistance due to long-term use of topical and systemic antibiotics as standard therapy for moderate to severe AV, isotretinoin has not been approved for widespread use in Indonesia. This causes another challenge in the management of AV. However, individual with AV might be benefited from adjuvant therapy which will work synergistically with the standard therapy and improve the outcome. Several adjuvant therapies can also reduce the side effect caused by standard therapy, such as irritation or dryness of the skin.[4] Various adjuvant therapy modalities include topical preparations, oral medication, diet modification, along with procedural treatments, such as comedone extraction, intralesional corticosteroid injection, chemical peeling, light and laser-based devices (Table 2).

TOPICAL THERAPY

Cleanser

Facial cleanser is a part of routine skin care used to remove dirt, sebum, dead cells, and bacteria.[5] The type of cleanser recommended for AV patients is a sebum-free cleanser containing synthetic detergents (syndets), astringents, and mild exfoliants. Beside its cleaning property, syndets does not change the normal pH of the skin. A randomized clinical trial (RCT) in Japan showed that mild cleansers can reduce AV lesions in 25% of adult with mild to moderate AV.[6] Addition of active ingredients such as triclosan, salicylic acid (SA), and azelaic acid were more effective in reducing inflammatory lesions up to 46% in another study and further maintaining remission even after its use was discontinued. The use of BP, SA, or sulfur is recommended and can be

an option for AV, especially in hard-to-reach areas at the back. Frequency of 2 times a day has been shown to be effective in reducing inflammatory and non-inflammatory AV lesions. More frequent use of facial cleanser can potentially increase skin pH, create damage on lipid layer as skin barrier and induce more irritant reaction while using topical anti-acne treatment.[5]

Moisturizer

Moisturizer use can overcome dryness and pain due to irritation caused by conventional therapy. Several moisturizing properties often used in various studies include dimethicone and glycerin which act as humectants. Hyaluronic acid can also act as humectant as well as counteract the stickiness from glycerin. Some herbal moisturizers also have anti-inflammatory effects, such as witch hazel leaf and aloe vera, while zinc-containing moisturizers have an effect on wound healing. General recommended moisturizers are non-comedogenic, hypoallergenic, non-irritating and working synergistically with conventional regimens, which will increase adherence to topical treatment.[5] Adherence to skin care regimen, including moisturizers was associated with a 2.2-fold increase in adherence of primary therapy, which was associated with an improvement in the number of AV lesions and its severity.[7] A split-face randomized clinical trial by Matsunaga et al.[8] showed that half face with administration of 0.1% adapalene accompanied by moisturizer showed better tolerance towards side effects, such as erythema, desquamation, xerosis, pain, and pruritus compared to the other side of the face that was not given moisturizer. A multicenter, double-blind, randomized, placebo-controlled study using nicotinamide with antibacterial adhesive agent and zinc-pyrrolidone carboxylic acid as adjuvant to adapalene was effective in reducing noninflammatory lesions by the second week of therapy without any significant different of adverse effect.[9]

Photoprotection

Recommendation of sunscreen is that which has photoprotective activity against ultraviolet A (UVA) and ultraviolet B (UVB) rays with a sun protection factor (SPF) of 30-50. Chemical sunscreens that absorb sunlight are more acceptable for patients with AV or oily skin types than physical sunscreens because they are water-based, easily absorbed without leaving any white casts. Facial cleansers, moisturizers, and sunscreens can help preparing skin to receive therapy and is part of routine skin care used during active lesion and remission.[3,4] A clinical trial using topical 5% BP with facial cleansers and moisturizers containing chemical sunscreen with SPF 30 showed 72% reduction of total lesion in 12 weeks.[8]

Table 1. Clinical classification of acne severity.[7]

	Severity		
	Mild	Moderate	Severe
Comedones	< 20	20-100	> 100
Papules / pustules	< 15	15-50	> 50
Nodules / cysts	0	< 5	> 5
Total lesions	< 30	30-125	> 125

Table 2. Recommendations of acne adjuvant therapy based on the level of evidence (LOE).

Modality	Severity of acne	LOE*
Topical therapy		
Cleanser, moisturizer and photoprotection	Mild to moderate acne	II
Antibacterial		
Triclosan	Mild to moderate acne	II
Sulfur	Mild to moderate acne	II
Tea tree oil	Mild to moderate acne	II
Anti-inflammatory		
Nicotinamide	Mild to moderate acne	II
Zinc	Mild to moderate acne	II
Witch hazel leaf extract	Mild to moderate acne	II
Comedolytic	Mild to moderate acne	II
Oral therapy		
Zinc	Mild to moderate acne	II
Lactoferrin	Mild to moderate acne	II
Levamisole	Mild to moderate acne	II
Antihistamine	Moderate to severe acne	II
Antioxidant	Mild to moderate acne	III
Metformin	Moderate to severe acne	II
Intralesional corticosteroid injection	Mild to moderate acne	III
Comedone extraction	Mild to moderate acne	II
Chemical peeling	Mild to moderate acne	II
Light and laser-based therapy		
Intense Pulse Light	Mild to severe acne	II
Photodynamic therapy	Mild to severe acne	I
Pulsed dye laser	Mild to moderate acne	I
Diode laser	Moderate to severe acne	I
1,550 nm Er:Glass fractional laser	Moderate to severe acne	I
1,320 nm Nd:YAG laser	Moderate to severe acne	II
1,064 nm Nd:YAG laser	Moderate to severe acne	II
Potassium titanyl phosphate (KTP) laser	Moderate to severe acne	II
Diet modification	Mild to moderate acne	II

Er:Glass: erbium glass, Nd:YAG: neodymium: yttrium aluminum garnet
LOE based on Oxford Center for Evidence-Based Medicine 2011

Sebum Control Agent

There are several topical ingredients that can control sebum production, consisting of retinol, retinaldehyde, alpha-hydroxy acids (AHA), beta-hydroxy acids (BHA) and polyhydroxy acids (PHA).[10] Retinol and retinaldehyde are vitamin A derivatives and retinoic acid precursors that work

by increasing epithelial keratinization. Vitamin A along with vitamin D can regulate inflammatory response to *P. acnes* colonization. SA, glycolic acid (GA), linoleic acid, lipo-hydroxy acid, and lauric acid can repair abnormal keratinization. Topical administrations of 0.1% retinaldehyde combined with 4% erythromycin and 6% GA are effective for the treatment of mild and moderate AV.[4]

Antimicrobial

Topical ingredients such as triclosan, sulfur, and tea tree oil (TTO) are often used because of their antibacterial effect which plays a role in reducing colonization of *P. acnes* and other bacteria that play a role in the pathogenesis of AV. Clinical trials of facial cleansers and gels containing TTO for 12 weeks showed reduction in total AV lesions.[10] Antibacterial adhesive agents (ABA) can reduce *P. acnes* colonization and attachment without risk of resistance.[3,4] In addition to antimicrobial properties, sulfur also show keratolytic effects due to its cysteine component. At market, sulfur is often combined with other agents, such as SA, BP, and resorcinol. The disadvantages of sulfur are its malodor and mild irritation which is often occurs when giving in combination with resorcinol.[11]

Anti-inflammatory

Topical anti-inflammatory drugs commonly used in AV include nicotinamide, zinc, and witch hazel leaf extract. Nicotinamide can act as monotherapy or in combination with clindamycin to improve AV lesions. Compare to clindamycin, nicotinamide monotherapy is equally effective in reducing total lesion and further risk of AV scars.[4] Topical zinc therapy can be given in the form of zinc acetate and zinc octoate. Zinc can also reduce *P. acnes* colonization by lipase inhibition and reducing free fatty acid levels.[12] Combination with topical erythromycin can increase antibiotic absorption while improving efficacy.[12]

Essential oils

Essential oils are volatile compound extracted from plant with unique scents. They are available in the forms of gel, spray, or paste. Several essential oils used as an adjuvant therapy for acne are tea tree oil, *Lactobacillus* Fermented *Chamaecyparis obtusa* (LFCO) leaf extract, copaiba, sandalwood oil, rosemary extract, jeju essential oil, Korean citrus, rosehip seed oil, frankincense oil, geranium oil, patchouli oil, peppermint oil, and neem oil. Tea tree oil, sandalwood oil, jeju essential oil, Korean citrus, frankincense oil, geranium oil, and peppermint oil have antimicrobial properties with inhibitory effects towards *P. acnes*. Copaiba, rosemary extract, rosehip seed oil, frankincense oil, patchouli oil, peppermint oil, and neem oil have anti-inflammatory properties. LFCO leaf extract has antimicrobial and sebosuppresive properties. In addition, these essential oils have antioxidant properties which will help maintain the skin health and prevent aging.[13,14]

SYSTEMIC THERAPY

Zinc

Oral preparations of zinc sulfate are more effective for severe AV than mild and moderate AV, but they are often accompanied by gastrointestinal side effects. Other oral preparations containing zinc gluconate have been shown to be useful in the management of inflammatory lesions. The use of zinc salts in few studies proven to be less effective than systemic tetracyclines, such as minocycline or oxytetracycline.[15] Administration of a methionine-bound zinc complex with antioxidants for three months followed by a month-free period of therapy can significantly reduce pustules, papules and closed comedones in mild to moderate AV.[16] Administration of zinc or in combination with nicotinamide may also be considered as an alternative treatment to reduce side effects and resistance to conventional antibiotics.[15]

Lactoferrin

Lactoferrin is a milk protein derivative which has been shown to have antibacterial and anti-inflammatory effects in vitro and in vivo. A double-blind RCT by Chan et al.[17] proved that administration of lactoferrin, zinc, and vitamin E three times a day for 3 months could reduce both inflammatory and non-inflammatory lesions compare to placebo. Effect of lactoferrin is thought to be based on combination of antibacterial, anti-inflammatory, and sebum control. Lactoferrin has bacteriostatic and bactericidal effects which also reduce proinflammatory cytokines, such as interleukin (IL)-8, IL-12 and IL-1β. Concurrent administration with zinc and vitamin E is thought to have a synergistic effect on overall AV improvement.[17]

Levamisole

Levamisole is an imidazothiazole derivative, anthelmintic with immunomodulatory properties. It is water-soluble and easily absorbed in gastrointestinal tract. Levamisole acts as an anti-inflammatory and immunomodulator by restoring function of damaged T-lymphocytes. The recommended dose is 2.5 mg/kg body weight per week up to a maximum of 150 mg. In a double-blind clinical trial, addition of levamisole to doxycycline 100 mg/day reduced total number of lesions, papules/pustules, nodules/cysts, and in general reduce severity of AV in 6 months more effectively than doxycycline alone.[18]

Antihistamines

Antihistamine as AV treatment is based on the discovery of a lot of histamine receptors in the sebaceous glands and it is believed to be involved as inflammatory mediators in AV. Combination of desloratadine and isotretinoin compared to isotretinoin alone was effective in reducing side effects of isotretinoin while reducing the number of AV lesions, sebum levels, and erythema in moderate and severe AV within 12 weeks with fewer side effects and relapse rates. It also improves AV severity, itch score, and overall quality of life.[19]

Antioxidant

Oxidative stress can cause follicular wall disruption of the sebaceous gland by producing free radicals, such as reactive oxygen species (ROS), nitric oxide, superoxide (SOD), and hydroxyl groups which justifies the use of antioxidants in AV treatment. Supplementation containing gamma linolenic acid, vitamin E, vitamin C, beta-carotene, coenzyme Q10, and *Vitis vinifera* in patients with nodular AV receiving isotretinoin medication can reduce isotretinoin side effects, including erythema and dry skin, while increased skin moisture.[20] Plant-based phytochemical also have antioxidant

property and can be potentially used as AV treatment, such as polyphenols, in the form of resveratrol, myricitrin, schisandrin, terchebulin, alpha-mangotin, curcumin, ellagic acid and epigallocatechin 3-gallate, as well as several alkaloids and terpenoids (berberine, ursolic acid, and lupeol). These various substances work as antioxidants through downregulation of hydrogen peroxide (H_2O_2), malondialdehyde (MDA), ROS, and upregulation of SOD. They also have anti-inflammatory, antibacterial effects against *P. acnes*, and antiandrogens properties, as well as decrease sebum production.[21] However, most of phytochemical studies on AV were carried out in preclinical trial.

Metformin

Increase in glycemic index is associated with increase of proinflammatory cytokines and its inflammatory process in AV. Cytokines, such as insulin growth factor (IGF-1) play a role in androgen synthesis and cause increase in sebum production. Metformin can be added as adjuvant in moderate to severe AV to reduce number of AV lesions. Effectiveness of metformin is thought to be related to inhibition of the mechanistic target of the rapamycin complex (mTORC1) which is activated by IGF-1. It is important to note that the use of metformin in these studies are limited to patients with altered metabolic parameters, such as fasting blood glucose levels, lipid profiles, abdominal circumference, and body mass index.[22]

INTRALESIONAL CORTICOSTEROID INJECTION

Intralesional injection of corticosteroids with anti-inflammatory effects is a part of standard therapy especially in moderate to severe AV and can act as an adjuvant for nodular AV lesions. The goal of intralesional injection is to maximize steroid concentration in the lesion while reducing the risk of systemic absorption. Recommended preparation is triamcinolone acetonide with dose of 0.05 to 0.25 ml for each lesion. It is highly useful in persistent nodular lesions and reducing risk of scar formation. Injection can be performed without incision or drainage. Side effects include hypopigmentation, especially in pigmented skin, skin atrophy, and telangiectasia.[23]

COMEDONE EXTRACTION

Comedone extraction was previously considered as a mainstay treatment of choice for superficial comedones and pustules. It is now indicated for comedone lesions that are unresponsive to comedolytic agents. Topical retinoid for 3 to 4 weeks before the procedure can help facilitate extraction and reduce risk of trauma.[21] Unna extractor is highly recommended because it has a wide flat plate and blunt edges to reduce the risk of trauma. Extraction of open comedones is indicated for cosmetic purpose, while closed comedones extraction is aimed at preventing rupture. In closed comedones, the orifice could be widened with a 25- or 30-gauge needle, lancet, scalpel no.11, superficial electrodesiccation, and a suction machine to help removing blackheads and other materials. Applicators, such as cotton buds, can be an alternative to removing the contents of the follicle. Prior to extraction, the skin area should be cleaned with antiseptic. Extractor should be placed in the center above the lesion and giving pressure perpendicularly. Incision and drainage under local anesthesia is indicated for persistent cysts followed by intralesional corticosteroids injection. Excision and marsupialization can also be performed for AV with sinus tract. In moderate AV with standard treatment using 0.05% tretinoin and 2.5% BP, adding comedone extraction as adjuvant therapy is equally effective to reduce inflammatory and non-inflammatory lesions as combination with oral antibiotics.[24]

CHEMICAL PEELING

Various studies have shown effectiveness of superficial chemical peeling on mild and moderate AV. Effectiveness of superficial chemical peeling is determined by patient's condition, severity of AV, active ingredients, concentration, also preparation before and after the procedure. Glycolic acid (GA) is classified as AHA group that improves keratinization of epidermal layer with concentrations of 30-70%. Addition of propylene glycol can reduce erythema. GA peel with 30% concentration was also proven in vivo to have bactericidal activity against *P. acnes*, which is beneficial in inflammatory lesions.[23] SA is a lipophilic beta hydroxy acid (BHA) with keratolytic and anti-inflammatory properties that can act specifically on pilosebaceous units. Study by Kessler et al.[26] found no significant difference between 30% GA and 30% SA for 12 weeks on AV improvement. SA has minimal side effects of erythema, dryness, and can be well tolerated by the patient and shows early improvement in comedones and papules. In addition, SA has whitening effect that is beneficial for post-acne hyperpigmentation.[22] Different with SA, AHA should be neutralized after application with bicarbonate. A recent randomized split face study found water can potentially use as a substitute for sodium bicarbonate plus solution in the neutralisation of 35% glycolic acid solution.[27]

Various clinical trials have shown the effectiveness of other chemical peelings, such as Jessner peel, lactic acid, pyruvic acid, trichloroacetic acid (TCA), amino fruit acid (AFA), pyruvic acid, and mandelic acid. Jessner peel contains 14% resorcinol, 14% SA, 14% lactic acid, and 95% ethanol 95 which acts as keratolytic, antibacterial, and anti-inflammatory agent. It is an option for Asian skin because of minimal side effects of hypopigmentation. AFA peel reduce non-inflammatory and inflammatory lesions significantly similar to GA peel with less irritation. Chemical peeling with TCA 25% is also proven to be effective as 30% SA. Pyruvic acid and mandelic acid also share similar effectiveness to 30% SA peel. Mandelic acid has anti-inflammatory and antimicrobial activity against *P. acnes*. Combination of peels can be more beneficial but should be monitored for its potential risk of post-peel complications.[28]

LIGHT AND LASER-BASED DEVICE

Light and laser-based therapy, such as Intense Pulsed Light (IPL), laser, and photodynamic therapy (PDT) aims to reduce sebum production and *P. acnes* colonization by porphyrin's light absorption produced by *P. acnes* in the sebaceous follicles. Coproporphyrin III

and protoporphyrin IX absorb light with wavelength of 400-700 nm, with 415 nm light waves or blue light being the most effectively absorbed. Photoexcitation of porphyrins causes formation of single oxygen and free radical reactions that are bactericidal against *P. acnes*. Red light with longer wavelength is not effective for porphyrin absorption, but penetrates deeper to sebaceous glands. These waves are phototoxic and photothermal to the sebaceous glands and induce anti-inflammatory cytokines that reduce inflammation. Blue light therapy, once a week for two weeks can improve severity of AV by up to 25%. Increased frequency of 2 times a week for 4 consecutive weeks can improve AV lesions up to 52%. If therapy continued for 12 weeks, it reduced inflammatory lesions by 63% and comedonal lesions by 45%. Combination therapy using both red and blue light had more reduction in AV lesions than blue light as a stand-alone treatment. Routine used for 12 weeks can reduce the number of inflammatory lesions by 76% and comedonal lesions by 58%.[29]

Mechanism of laser-based device depends on the wavelength produced. Laser utilizing red light, such as erbium glass (Er:Glass) with 1,550 nm and neodymium: yttrium aluminum garnet (Nd:YAG) 1,320 nm and 1,064 nm can penetrate into dermis and cause minimal damage on epidermal layer. Diode laser, pulsed dye laser (PDL), and potassium titanyl phosphate (KTP) have different mechanism by targeting on water and delivering heat to deeper layers of the dermis without affecting epidermis and its superficial layer. PDL reduces sebum production by increasing temperature of sebaceous glands, while KTP laser works by activating light from porphyrins which further reduce *P. acnes* colonization. Use of 1,550 nm Er:Glass fractional laser led to reduction in AV lesions, sebaceous gland size, increased overall remission and is recommended for active lesion with a total of 1-4 sessions.[28] The use of cooling system also increases the efficacy with milder side effects, such as temporary erythema. Dual mode method with 4 to 5 passes all over the face with low-fluence, 5 to 6 J/cm^2 has fewer side effects compared to higher fluency (14-15 J/cm^2). PDL 595 nm also reduces number of AV lesions, severity of AV, and erythema in mild to moderate AV with side effects of hypopigmentation and postoperative pain. KTP laser 532 nm improves AV lesion and can be given once in a or two weeks. Diode laser 1,450 nm effectively reduce AV lesions by up to 63% in 10 weeks and is well tolerated.[29]

Photodynamic therapy (PDT) is a combination of light-based therapy with photosensitizers, such as aminolevulinic acid (ALA), methylaminolevulinic acid (MAL) esters and liposomal methylene blue (LMB). However, several studies did not find significant differences of efficacy between PDT and light-based therapy or topical treatment alone. Efficacy however can be affected by different concentrations of photosensitizers. MAL-PDT activated by red light improved total lesion count compared to placebo cream. The use of indocyanine green in photodynamic therapy has bactericidal effect against *P. acnes*. However, different types of PDT, frequency, and patient populations in various studies should be considered before drawing conclusion of its meta-analysis. The AV consensus in Southeast Asia recommends combination of 5-ALA and blue and red-light IPL as adjunctive therapy for severe AV. The use of IPL as monotherapy is less effective than PDT, but can be used in patients who cannot tolerate side effects of PDT.[30]

DIET MODIFICATION

Increase consumption of food with high glycemic index is associated with AV and increasing severity. Food with high glycemic index will increase proinflammatory cytokines and cause inflammatory process in AV. Diet modification can reduce sebaceous glands size, inflammation, expression of sterol regulatory element-binding protein-1 and IL-8. It also promotes weight loss, improved body mass index and insulin sensitivity. Diet modification consisting of 45% calories from carbohydrates with a low glycemic load, 25% protein and 30% fat act as an adjuvant therapy for AV to a topical 2.5% BP gel and facial cleanser in reducing total AV lesions.[31]

CONCLUSION

There are various modalities of adjuvant therapy in AV, consisting of topical agent, systemic medication, comedone extraction, intralesional corticosteroid injection, chemical peeling, light and laser-based therapy, and diet modification. These various modalities combined with standard treatment have good efficacy and relatively well-tolerated. Use of adjuvant therapy can work synergistically with the standard treatment to increase effectiveness while reducing side effects of standard therapy. Further research is needed on some adjuvant therapies in order to provide recommendations for use in clinical practice.

CONFLICT OF INTEREST

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AUTHORS CONTRIBUTIONS

All authors contributed in the literature review, manuscript construction, and publication.

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