JDA Japanese Dermatological Association
The Journal of Dermatology

doi: 10.1111/1346-8138.14355 *Journal of Dermatology* 2018; **45**: 898–935

GUIDELINE

Japanese Dermatological Association Guidelines: Guidelines for the treatment of acne vulgaris 2017

Nobukazu HAYASHI,[1] Hirohiko AKAMATSU,[2] Keiji IWATSUKI,[3] Ryoko SHIMADA-OMORI,[4] Chikako KAMINAKA,[5] Ichiro KUROKAWA,[6] Takeshi KONO,[7] Miwa KOBAYASHI,[8] Miki TANIOKA,[9] Fukumi FURUKAWA,[10] Minao FURUMURA,[11] Osamu YAMASAKI,[3] Kenshi YAMASAKI,[4] Yuki YAMAMOTO,[5] Yoshiki MIYACHI,[12] Makoto KAWASHIMA[13]

[1]*Department of Dermatology, Toranomon Hospital, Tokyo,* [2]*Applied Cell and Regenerative Medicine, Fujita Health University School of Medicine, Aichi,* [3]*Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama,* [4]*Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai,* [5]*Department of Dermatology, Wakayama Medical University, Wakayama,* [6]*Department of Dermatology, Meiwa Hospital, Nishinomiya,* [7]*Department of Dermatology, Chiba Hokusoh Hospital, Nippon Medical School, Inba-gun,* [8]*Kobayashi Dermatology Clinic, Kitakyushu,* [9]*Tanioka Dermatology Clinic, Kyoto,* [10]*Takatsuki Red Cross Hospital, Takatsuki,* [11]*Section of Dermatology, Department of Medicine, Fukuoka Dental College, Fukuoka,* [12]*Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto,* [13]*Department of Dermatology, Tokyo Women's Medical University, Tokyo, Japan*

ABSTRACT

The Guidelines for the Treatment of Acne Vulgaris of the Japanese Dermatological Association was first published in Japanese in 2008 and revised in 2016 and 2017. These guidelines (GL) indicate the standard acne treatments in Japan and address pharmaceutical drugs and treatments applicable or in use in Japan. In these GL, the strength of the recommendation is based on clinical evidences as well as availability in Japanese medical institutions. In the 2016 and 2017 GL, some of the clinical questions were revised, and other questions were added in accordance with approval of topical medicines containing benzoyl peroxide (BPO). Rather than monotherapies of antibiotics, the 2017 GL more strongly recommend combination therapies, especially fixed-dose combination gels including BPO in the aspects of pharmacological actions and compliance in the acute inflammatory phase to achieve earlier and better improvements. The 2017 GL also indicate to limit the antimicrobial treatments for the acute inflammatory phase up to approximately 3 months and recommend BPO, adapalene, and a fixed-dose combination gel of 0.1% adapalene and 2.5% BPO for the maintenance phase to avoid the emergence of antimicrobial-resistant *Propionibacterium acnes*. The 2017 GL also discuss rosacea, which requires discrimination from acne and a different treatment plan.

Key words: **acne vulgaris, antimicrobial resistant, guideline, maintenance therapy, *Propionibacterium acnes*.**

BACKGROUND FOR THE FORMULATION AND REVISION OF THESE GUIDELINES

Acne vulgaris is a chronic inflammatory disease caused by the complex influences of abnormal lipid metabolism (endocrine factors), abnormal keratinization and bacterial proliferation. It affects pilosebaceous units on the face, chest and back during and after puberty. As this disease affects at least 90% of the Japanese population, it is said that "acne is a symbol of youth" and dismissed as a physiological phenomenon. It has therefore not been properly acknowledged as a skin disease. This is why less than 10% of patients suffering from acne receive medical treatment, and treated patients are frequently unsatisfied. At the same time, there are data suggesting that even mild acne symptoms may leave scars and early treatment can prevent scarring. Considering that the quality of life (QOL) of acne patients are disturbed, and acne is a potential cause for bullying among junior and senior high school students, aggressive treatment in the early inflammatory stage and post-inflammation maintenance therapy are recommended.

The Guidelines for the Treatment of Acne Vulgaris 2008 were formulated, reflecting a growing interest in acne treatment, against a background of acne treatment increasingly being conducted by doctors with little dermatological

Correspondence: Nobukazu Hayashi, M.D., Ph.D., Department of Dermatology, Toranomon Hospital, 2-2-2 Toranomon, Minato-ku, Tokyo 105-8470, Japan. Email: hayashi@toranomon.gr.jp

This is the secondary English-language publication of the original Japanese manuscript for the "Guidelines for the treatment of acne vulgaris 2017", published in the Japanese *Journal of Dermatology* (127:1261–1302, 2017).
Received 14 March 2018; accepted 15 March 2018.

experience including non-dermatologists into the field of cosmetic dermatology. The guidelines can be considered to have achieved their initial goal, of pre-empting confusion in Japanese acne treatment and improving the quality of treatment, by suggesting appropriate and standardized criteria for deciding on treatment based on evidence.

Conventional acne treatment in Japan primarily targeted the inflammatory acne lesions, and focused on the use of antimicrobials for topical and systemic treatments. The introduction of adapalene in 2008, which is the first treatment of comedone covered by health insurance in Japan, greatly contributed to the development of acne treatment. Moreover, the conceptualization of microcomedones, the histopathological change and precursors of comedones that accumulate sebum in hair follicles, allowed for the idea of maintenance therapy for comedones and microcomedones once inflammation subsides. Furthermore, the introduction of benzoyl peroxide (BPO), on the request of the Japanese Dermatological Association (JDA), made it possible to avoid increases in drug-resistant *Propionibacterium acnes*.

The Guidelines for the Treatment of Acne Vulgaris 2016 implemented additional measures to streamline antimicrobial treatment, for maintenance therapy and to avoid increases in drug-resistant bacteria, thus aiming to further improve the quality of treatment. These guidelines also discussed rosacea, which requires discrimination from acne and a different treatment plan. After the subsequent approval and sales of fixed-dose combination gel of 0.1% adapalene and 2.5% BPO, Clinical Questions (CQ) on the combined use of adapalene and BPO were deleted from the Guidelines for the Treatment of Acne Vulgaris 2017, and were replaced with CQ on fixed-dose combination gel. Moreover, a CQ regarding oral contraceptives and low-dose estrogen progestin was revised based on the 2015 Oral Conceptive (OC) and Low-dose-estrogen-progestin (LEP) Guidelines from the Japan Society of Obstetrics and Gynecology.

STATUS OF THESE GUIDELINES

The Revision Committee for these guidelines consists of committee members and practitioners appointed by the JDA. The committee had convened on four occasions since September 2014 at the time of the 2016 guidelines revision. The current revision was publicly announced after the committee had convened once, as well as conducted several email deliberations, followed JDA procedures, solicited public comments, and gained the approval of JDA's Guidelines Committee and Board of Directors.

Although these guidelines indicate the current standard for the treatment of acne vulgaris in Japan, difference in symptom severity, diversity of complications and background of each patient should be taken into consideration. This ensures that any actual treatment is decided on by the responsible doctor together with the patient, meaning that the treatment does not necessarily have to conform to these guidelines completely. These guidelines also do not cover acne conglobata, acne fulminans, synovitis, acne, pustulosis, hyperostosis and osteitis syndrome, pyogenic arthritis, pyoderma gangrenosum and acne syndrome, and similar conditions.

FUNDING AND CONFLICTS OF INTEREST

The costs associated with the revision of these guidelines has been covered in full by the JDA. With respect to conflicts of interest (COI) in the 1-year period before 1 October 2015, Nobuzaku Hayashi, Hirohiko Akamatsu and Kenshi Yamasaki received lecture fees from Maruho Co., Ltd.; Makoto Kawashima received medical expert remuneration and lecture fees from Maruho Co., Ltd. and GlaxoSmithKline plc; and Yoshiki Miyachi received Maruho Prize money awarded by Maruho Co., Ltd. and medical expert remuneration from Galderma S.A. Furthermore, the institute to which Kenshi Yamasaki and Ryoko Shimada-Omori belong is in receipt of donations from Maruho Co., Ltd. and Tokiwa Pharmaceutical Co., Ltd. Fukumi Furukawa, Yuki Yamamoto, and Chikako Kaminaka also belong to an institute in receipt of donations from JMEC Co., Ltd. In connection with this revision, Nobukazu Hayashi, Keiji Iwatsuki, Makoto Kawashima, Ichiro Kurokawa, Miwa Kobayashi, Yoshiki Miyachi and Kenshi Yamasaki have COI regarding fixed-dose combination gel containing adapalene 0.1% and BPO 2.5% for the 1-year period before 30 September 2016. There were no committee members with COI regarding oral contraceptives or low-dose estrogen progestin combination drugs. There was no one else to whom JDA regulations for COI were applicable due to being in receipt of remuneration from individuals or organizations involved in the development or sales of drugs and medical equipment discussed in these guidelines. Committee members who had participated in the development of, or have COI due to, relevant designated drugs, did not join the judgments on those drugs' recommendation decisions.

COLLECTION OF EVIDENCE

Databases referred to were PubMed, Japanese Medical Abstracts Society Web and Cochrane Database of Systematic Reviews.

Search period: We targeted references that were searchable until February 2015 (August 2016 for entries revised in 2017). Important references published later were added as appropriate.

Selection criteria: We prioritized papers that had passed a systematic review of randomized controlled trials (RCT) or RCT. If such papers were not available, we selected papers based on cohort studies, case–control studies or other similar studies. We also referenced a part of case-series studies. We excluded references based on basic experiments.

CRITERIA FOR THE DETERMINATION OF CQ SELECTION, EVIDENCE LEVEL AND STRENGTH OF RECOMMENDATION

These guidelines indicate the standard for acne treatment in Japan and address pharmaceutical drugs and treatments applicable or in use in Japan in the form of CQ. We also created CQ on ingredients contained in cosmetics as well as

skincare, lifestyle and similar factors. We deleted or changed the contents of those CQ for which evidence could not be gathered or could be obtained only in part.

We created evidence levels and strength of recommendation decision criteria with reference to the criteria adopted in the JDA Guidelines for the Treatment of Skin Cancer.

Most acne treatments are covered by the National Health Insurance system in Japan. With regard to ingredients contained in cosmetics and some treatments not covered by health insurance in Japan, we took into consideration the strength of recommendation decision. This made it difficult to strongly recommend or otherwise promote them in these Guidelines for the Treatment of Acne Vulgaris, unless there were RCT results that clearly showed cosmetics to be on par with or superior to pharmaceutical drugs in Japan. Even when they had passed RCT, we chose to present them as an alternative. As such, we changed C1 from "Recommended as an alternative despite a lack of high-quality evidence" to "Recommended as an alternative." Moreover, treatments for which the evidence shows an effectiveness corresponding to A, but which are inferior when considering adverse events, have been given the grade A*.

Evidence level classifications

LI. Systematic reviews, meta-analyses.
LII. One or more RCT.
LIII. Non-RCT (including before-and-after trials with statistical analyses).
LIV. Analytical–epidemiological studies (cohort studies and case–control studies).
LV. Descriptive studies (case reports and case-series studies).
LVI. The opinions of expert committee members and individual experts.

Strength of recommendation classifications

A: Strongly recommended for use (there is at least one instance of LI evidence or high-quality LII evidence showing its effectiveness).
A*: Recommended for use (there is evidence of effectiveness corresponding to A, but its strength of recommendation is inferior when taking into account adverse events).
B: Recommended for use (there is at least one instance of low-quality LII evidence, high-quality LIII evidence or extremely high-quality LIV evidence showing its effectiveness).
C1: Recommended as an alternative (there is low-quality LIII–IV evidence, multiple instances of high-quality LV evidence or LVI evidence approved by the committee).
C2: Not recommended due to insufficient evidence (at present).
D: Discouraged for use (there is high-quality evidence that it is ineffective or harmful).

PRE-PUBLICATION REVIEW

The JDA's Guidelines Committee solicited public comments from representatives before the general publication of these guidelines and made changes where necessary.

UPDATE PLAN

We expect these guidelines to be updated in 5 years.

DEFINITIONS

"Acne": A chronic inflammatory disease affecting pilosebaceous units, that first appears as comedones, and may cause red papules, pustules and nodulocystic lesions. It may also leave scars after inflammation has subsided.

"Comedones": A condition of the sebaceous follicles induced by the accumulation of sebum in the follicles. This is due to an increase in sebum secretion following heightened sebaceous gland activity, as well as exacerbated keratinization in follicular infundibulum. Comedones are categorized depending on whether the pores are closed or open, as either closed comedones (whitehead) or open comedones (blackhead).

"Microcomedones": A histopathological change that precedes acne lesions. The follicles are closed with accumulated sebum inside. It is also known that they may be found in the proximity of acne lesions even without clinical symptoms. Microcomedones therefore require maintenance therapy that provides appropriate treatment continuously.

"Inflammatory acne lesions": Includes red papules and pustules (with areola and erythema) that accompany acne. Papules with a diameter of more than 5 mm are sometimes called nodules.

"Nodulocystic lesions": Refers to the cysts and indurations that accompany the severe inflammation of exceptionally serious cases of acne.

"Post-inflammatory erythema": Refers to erythema that remains temporarily after an inflammatory acne lesion has subsided and signs of inflammation have disappeared.

"Nodulocystic lesions without inflammation": Refers to the cysts or fibrotic lesions that remain after an acne lesion has subsided and inflammation has disappeared, in the case of severe inflammation accompanied by cysts and indurations.

"(Acne) scars": Refers to the depressions (i.e. atrophic or depressed scars), elevations (including hypertrophic scars and keloids), and hyperpigmentation in the skin that appear after inflammatory acne lesions and other acne lesions have subsided.

"Acute inflammatory phase": This is characterized by inflammatory acne lesions accompanied by comedones. This phase requires aggressive treatment of the inflammation. Acute inflammatory phase treatment usually lasts a maximum of 3 months and is followed by the maintenance phase.

"Maintenance phase": This is the phase after the inflammatory acne lesions have subsided. It is characterized by comedones or microcomedones, at times accompanied by slight inflammation with a few inflammatory acne lesions or erythema with pathological inflammation that appears during and after the recession of inflammatory acne lesions. To maintain the state of subsided inflammation, comedones and microcomedones should be treated continuously, whereas relapsing or continuous inflammatory acne lesions should be treated using drugs that do not risk introducing resistant bacteria.

"Grade of severity": We followed the acne severity grading criteria for Japanese acne patients,[1] created by the Acne Research Society, which consists of volunteer dermatologists. These criteria focus on cases characterized by inflammatory acne lesion counting and global assessment using photographs. The grading criteria by inflammatory lesion counting are as follows: "mild", five or fewer eruptions on half the face; "moderate", between 6 and 20 eruptions on half the face; "severe", between 21 and 50 eruptions on half the face; and "very severe", 51 or more eruptions on half the face.

"Rosacea": A chronic inflammatory disease with unknown causes that appears mainly on the face in middle and old age. It features the separate or mixed appearances of erythematotelangiectatic rosacea (subtype 1, erythematous rosacea), with symptoms of erythema, enlarged capillaries and a burning sensation, sometimes referred to as "red face"; papulopustular rosacea (subtype 2, acne rosacea), with the acne-like principal symptoms of papules and pustules, but with no accompanying comedones; phymatous rosacea (subtype 3), which causes the nose to swell; and ocular rosacea (ocular complication), which is accompanied by hyperemia and inflammation of the eyelid and eyeball conjunctiva. Unlike acne, there are no comedones. Ultraviolet (UV) light, sudden changes in air temperature, stimulating food and alcohol intake are known exacerbating factors.

"RCT": Short for randomized controlled trial. A clinical trial where the participants are randomly divided into a group that receives intervention and a control group for the purpose of reducing data bias. This is the same as a randomized comparative trial.

"Cohort study": A research method where information is gathered about a group of people in possession of a certain factor, and about a group not in possession of the same factor, after which the prevalence of diseases and other factors in the two groups is traced.

"Case–control study": A research method for determining causes of disease, where past disclosed factors are compared between individuals with a specific disease (the patients) and individuals without the disease.

"Case-series study": A report that collates a large number of cases of the same disease.

"*P. acnes*": Short for *Propionibacterium acnes*. This is a lipophilic and facultative anaerobic bacillus that resides in the skin, especially the hair follicles. It becomes a causative agent when proliferating in comedones, causing inflammatory acne lesions. Fearing the appearance of drug-resistant *P. acnes* due to long-term use of antimicrobials, it has become an urgent task in recent years to avoid the long-term use of antimicrobials.

REFERENCE

1 Hayashi N, Akamatsu H. Kawashima M; Acne Study Group. Establishment of grading criteria for acne severity. *J Dermatol* 2008; **35**: 255–260.

CQ OVERVIEW

Table 1 displays the CQ with strengths of recommendation and recommendations. CQ are categorized as inflammatory acne lesions during the acute inflammatory phase, comedones, nodulocystic lesions with inflammation, maintaining remission, scars, general acne, and skincare and related treatments, with subheadings such as topical treatments, oral treatments, and others. We have prioritized entries with higher strengths of recommendation. Antimicrobials are arranged by category, *Kampo* (traditional herbal medicine) by health insurance coverage in Japan, and others in alphabetical order based on their general or generic names. We have also included entries on rosacea.

TREATMENT ALGORITHM

Figure 1 shows a revised treatment algorithm on the basis of CQ strengths of recommendation and recommendations. It is classified into the acute inflammatory phase and the maintenance phase. For the very severe acne in the acute inflammatory phase, the committee decided to recommend treatments as they had been recommended for severe acne, even when no clinical trials had been conducted for very severe acne.

Regarding topical drugs in the acute inflammatory phase, fixed combination and combined-use therapies were superior to monotherapy because they have more pharmacological actions. Of the two, fixed combination therapy was placed at the top in the aspect of compliance. The committee did not evaluate the relative superiority between two fixed-dose combination drugs.

Composition and roles of the guidelines for the treatment of acne revision committee

Table 2 shows the committee's composition and roles as well as the extent of evidence-gathering responsibilities.

STRENGTHS OF RECOMMENDATION, RECOMMENDATIONS AND COMMENTS

CQ1: Is fixed-dose combination gel of clindamycin (CLDM) 1% and BPO 3% effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend fixed-dose combination gel of CLDM 1% and BPO 3% (CLDM1%/BPO3%) to treat inflammatory acne lesions (moderate to severe).

Comments: For fixed-dose combination gel of CLDM1%/BPO3%, both CLDM and BPO have an antimicrobial effect on *P. acnes*. CLDM also has an anti-inflammatory effect.[2]

Two high-quality LII references (one overseas, one Japanese) show the clinical effectiveness of this treatment for inflammatory acne lesions.[3,4] These investigations studied acne patients with moderate to severe inflammatory acne lesions during a treatment period of 12 weeks, and covered 1315[3] and 800[4] cases, respectively. Both trials reported significant improvements to grades of severity evaluated by attending doctors and significant reductions to inflammatory acne lesions.[3,4] In the former, CLDM1%/BPO3% (once a day) was shown to significantly reduce the number of inflammatory and other acne lesions more effectively than CLDM 1% gel (once a day), BPO 3% gel (once a day), and placebo.[3] In the latter, the topical application of CLDM1%/BPO3% once or twice a day was shown to

Table 1. Overview of clinical questions 2017

Inflammatory acne lesions during the acute inflammatory phase				
Topical treatments	CQ1	Is fixed-dose combination gel of clindamycin (CLDM) 1% and benzoyl peroxide (BPO) 3% effective for inflammatory acne lesions?	A	We strongly recommend fixed-dose combination gel of CLDM 1% and BPO 3% to treat inflammatory acne lesions (moderate to severe)
	CQ2	Is fixed-dose combination gel of adapalene 0.1% and BPO 2.5% effective for inflammatory acne lesions?	A	We strongly recommend fixed-dose combination gel of adapalene 0.1% and BPO 2.5% to treat inflammatory acne lesions (moderate to very severe)
	CQ3	Is the combined use of adapalene 0.1% gel together with a topical antimicrobial effective for inflammatory acne lesions?	A	We strongly recommend the combined use of adapalene 0.1% gel together with a topical antimicrobial to treat inflammatory acne lesions (mild to severe)
	CQ4	Is BPO 2.5% gel effective for inflammatory acne lesions?	A	We strongly recommend BPO 2.5% gel to treat inflammatory acne lesions (mild to moderate)
	CQ5	Is adapalene 0.1% gel effective for inflammatory acne lesions?	A	We strongly recommend adapalene 0.1% gel to treat inflammatory acne lesions (mild to severe)
	CQ6	Are topical antimicrobials effective for inflammatory acne lesions?	A	We strongly recommend topical antimicrobials (CLDM, nadifloxacin and ozenoxacin) to treat inflammatory acne lesions
	CQ7	Is the combined use of fixed-dose combination gel containing adapalene 0.1% and BPO 2.5% together with an oral antimicrobial effective for inflammatory acne lesions?	A	We strongly recommend the combined use of fixed-dose combination gel containing adapalene 0.1% and BPO 2.5% together with an oral antimicrobial to treat inflammatory acne lesions (moderate to very severe)
	CQ8	Is the combined use of adapalene 0.1% gel together with an oral antimicrobial effective for inflammatory acne lesions?	A	We strongly recommend the combined use of adapalene 0.1% gel together with an oral antimicrobial to treat inflammatory acne lesions (moderate to very severe)
	CQ9	Are topical non-steroidal anti-inflammatory drugs (NSAIDs) effective for inflammatory acne lesions?	C1	We recommend ibuprofen piconol cream as an alternative to treat inflammatory acne lesions (mild to moderate)
	CQ10	Are topical steroids effective for inflammatory acne lesions?	C2	We do not recommend topical steroids to treat inflammatory acne lesions
Oral treatments	CQ11	Are oral antimicrobials effective for inflammatory acne lesions?	A, A*, B or C1	We strongly recommend oral antimicrobials to treat inflammatory acne lesions
		Doxycycline	A	We strongly recommend oral doxycycline to treat inflammatory acne lesions
		Minocycline	A*	We recommend oral minocycline to treat inflammatory acne lesions
		Roxithromycin	B	We recommend oral roxithromycin to treat inflammatory acne lesions
		Faropenem	B	We recommend oral faropenem to treat inflammatory acne lesions
		Tetracycline	C1	We recommend oral tetracycline as an alternative to treat inflammatory acne lesions
		Erythromycin	C1	We recommend oral erythromycin as an alternative to treat inflammatory acne lesions
		Clarithromycin	C1	We recommend oral clarithromycin as an alternative to treat inflammatory acne lesions

Table 1. (continued)

		Levofloxacin	C1	We recommend oral levofloxacin as an alternative to treat inflammatory acne lesions
		Tosufloxacin	C1	We recommend oral tosufloxacin as an alternative to treat inflammatory acne lesions
		Ciprofloxacin	C1	We recommend oral ciprofloxacin as an alternative to treat inflammatory acne lesions
		Lomefloxacin	C1	We recommend oral lomefloxacin as an alternative to treat inflammatory acne lesions
		Cefuroxime axetil	C1	We recommend oral cefuroxime axetil as an alternative to treat inflammatory acne lesions
	CQ12	Is *Kampo* (traditional herbal medicine) effective for inflammatory acne lesions?	C1 or C2	We recommend *Keigairengyoto*, *Seijobofuto* and *Jumihaidokuto* as alternatives to treat inflammatory acne lesions, if other treatments are ineffective or cannot be implemented. *Orengedokuto*, *Unseiin*, *Unkeito* and *Keishibukuryogan* may be used, but we do not recommend them
			Keigairengyoto, *Seijobofuto*, *Jumihaidokuto*	C1
			Orengedokuto, *Unseiin*, *Unkeito*, *Keishibukuryogan*	C2
	CQ13	Are oral steroids effective for the very severe inflammatory acne lesions?	C2	We do not recommend oral steroids to treat the very severe inflammatory acne lesions
	CQ14	Is oral DDS (diaminodiphenyl sulfone, dapsone) effective for inflammatory acne lesions?	C2	We do not recommend oral DDS to treat inflammatory acne lesions
	CQ15	Are oral NSAIDs effective for inflammatory acne lesions?	C2	We do not recommend oral NSAIDs to treat inflammatory acne lesions
Other Treatments	CQ16	Is chemical peeling effective for inflammatory acne lesions?	C1 or C2	We recommend chemical peeling using glycolic acid or salicylic acid in macrogol as an alternative to treat inflammatory acne lesions, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan
		Glycolic acid	C1	We recommend chemical peeling using glycolic acid as an alternative to treat inflammatory acne lesions, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan
		Salicylic acid in macrogol	C1	We recommend chemical peeling using salicylic acid in macrogol as an alternative to treat inflammatory acne lesions, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan

Table 1. (continued)

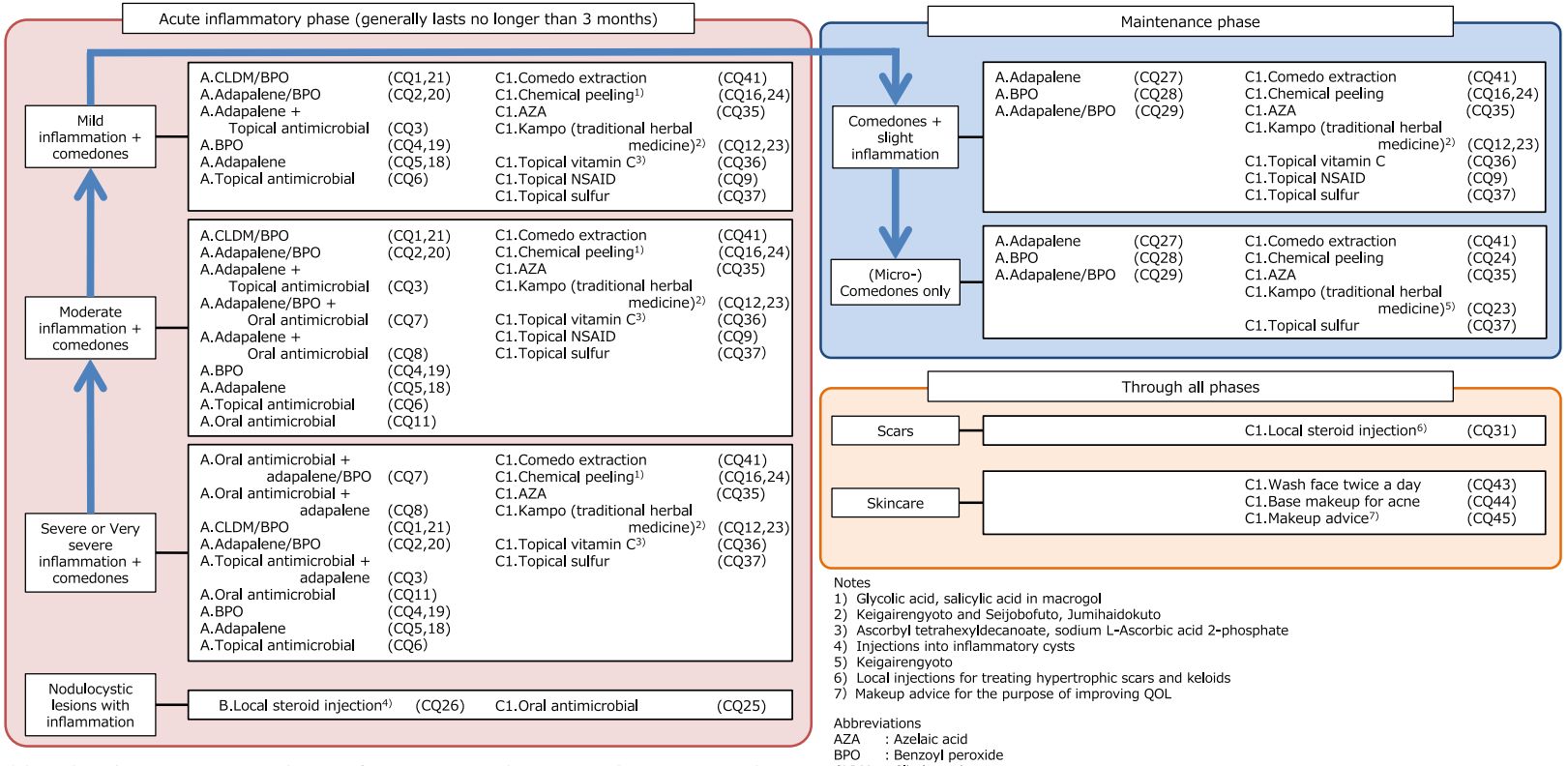
		Salicylic acid in ethanol	C2	We currently do not recommend chemical peeling using salicylic acid in ethanol to treat inflammatory acne lesions. It must also be taken into consideration that this is not covered by health insurance in Japan
	CQ17	Is phototherapy effective for inflammatory acne lesions?	C2	Blue light phototherapy may be used to treat inflammatory acne lesions (mild to moderate) and photodynamic therapy to treat inflammatory acne lesions (moderate to severe). However; considering equipment and drug issues, as well as a lack of review in Japan and a lack of cover by health insurance in Japan, we do not recommend it
Comedones				
Topical treatments	CQ18	Is adapalene 0.1% gel effective for comedones?	A	We strongly recommend adapalene 0.1% gel to treat comedones
	CQ19	Is BPO 2.5% gel effective for comedones?	A	We strongly recommend BPO 2.5% gel to treat comedones
	CQ20	Is fixed-dose combination gel of adapalene 0.1% and BPO 2.5% effective for comedones?	A	We strongly recommend fixed-dose combination gel of adapalene 0.1% and BPO 2.5% to treat comedones
	CQ21	Is fixed-dose combination gel of CLDM 1% and BPO 3% effective for comedones?	A	We strongly recommend fixed-dose combination gel of CLDM 1% and BPO 3% to treat comedones with inflammatory acne lesions. However, we do not recommend it for maintenance therapy after the inflammatory acne lesions have subsided
	CQ22	Are topical antimicrobials effective for comedones?	C2	We do not recommend topical antimicrobials to treat comedones
Oral treatments	CQ23	Is *Kampo* effective for comedones?	C1 or C2	We recommend *Keigairengyoto* as an alternative to treat comedones, if other treatments are ineffective or cannot be implemented. *Orengedokuto*, *Jumihaidokuto* and *Keishibukuryogan* may be used, but we do not recommend them
		Keigairengyoto	C1	
		Orengedokuto, *Jumihaidokuto*, *Keishibukuryogan*	C2	
Other Treatments	CQ24	Is chemical peeling effective for comedones?	C1 or C2	We recommend chemical peeling using glycolic acid or salicylic acid in macrogol as an alternative to treat comedones, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan
		Glycolic acid	C1	We recommend chemical peeling using glycolic acid as an alternative to treat comedones, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan
		Salicylic acid in macrogol	C1	We recommend chemical peeling using salicylic acid in macrogol as an alternative to treat comedones, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan
		Salicylic acid in ethanol	C2	We currently do not recommend chemical peeling using salicylic acid in ethanol to treat comedones. It must also be taken into consideration that this is not covered by health insurance in Japan

Table 1. (continued)

Nodulocystic lesions with inflammation				
Oral treatments	CQ25	Are oral antimicrobials effective for nodulocystic lesions with inflammation?	C1	We recommend oral antimicrobials as an alternative to treat nodulocystic lesions with inflammation
Injections	CQ26	Are local steroid injections effective for nodulocystic lesions with inflammation?	B	We recommend local steroid injections into the cysts with inflammation
Maintaining remission				
Topical treatments	CQ27	Is adapalene 0.1% gel effective for maintaining remission after inflammation has subsided?	A	We strongly recommend adapalene 0.1% gel for maintaining remission after inflammation has subsided
	CQ28	Is BPO 2.5% gel effective for maintaining remission after inflammation has subsided?	A	We strongly recommend BPO 2.5% gel for maintaining remission after inflammation has subsided
	CQ29	Is fixed-dose combination gel of adapalene 0.1% and BPO 2.5% effective for maintaining remission after inflammation has subsided?	A	We strongly recommend fixed-dose combination gel of adapalene 0.1% and BPO 2.5% for maintaining remission after inflammation has subsided
Scars				
Oral treatments	CQ30	Is oral tranilast effective for hypertrophic acne scars?	C2	Oral tranilast may be used to treat hypertrophic acne scars, but we do not recommend it
Injections	CQ31	Are local steroid injections effective for hypertrophic acne scars?	C1	We recommend local steroid injections as an alternative to treat hypertrophic acne scars
	CQ32	Are filler injections effective for atrophic acne scars?	C2	Filler injections (collagen, hyaluronic acid) may be used to treat atrophic acne scars, but we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan
Other Treatments	CQ33	Is chemical peeling effective for atrophic acne scars?	C2	Chemical peeling using trichloroacetic acid or concentrated glycolic acid may be used to treat atrophic acne scars, but we do not recommend it. It must also be taken into consideration that this is not covered by health insurance in Japan
	CQ34	Is surgical intervention effective for hypertrophic acne scars and keloids?	C2	Surgical excision and cryotherapy may be used to treat hypertrophic acne scars and keloids, but we do not recommend them
General acne				
Topical treatments	CQ35	Is topical azelaic acid effective for comedones and inflammatory acne lesions?	C1	We recommend topical azelaic acid as an alternative to treat comedones and inflammatory acne lesions. However, it must be taken into consideration that this is not covered by health insurance in Japan
	CQ36	Is topical vitamin C effective for inflammatory acne lesions and post-inflammatory erythema?	C1	We recommend topical ascorbyl tetrahexyldecanoate and sodium L-ascorbyl-2-phosphate as an alternative to treat inflammatory acne lesions and post-inflammatory erythema. However, it must be taken into consideration that they are not covered by health insurance in Japan
	CQ37	Is topical sulfur preparation effective for acne?	C1	We recommend topical sulfur preparation as an alternative to treat acne
Oral treatments	CQ38	Are oral contraceptives and low-dose estrogen progestin combination drugs effective for acne?	C2	Oral contraceptives and low-dose estrogen progestin combination drugs may be used to treat acne, if other treatments are insufficient and the adult female patient agrees to the resulting risk of contraception, but we do not recommend them. Because they are unapproved treatments for acne that are not covered by health insurance in Japan

Table 1. (continued)

				and may cause adverse events such as thrombosis and abnormal vaginal bleeding, sufficient informed consent is required
	CQ39	Is spironolactone effective for acne?	C2	We do not recommend oral spironolactone to treat acne characterized by either inflammatory acne lesions or comedones
	CQ40	Are oral vitamins effective for acne?	C2	Oral vitamins may be used to treat acne, but we do not recommend them
Other Treatments	CQ41	Is comedo extraction effective for comedones and inflammatory acne lesions?	C1	We recommend comedo extraction as an alternative to treat comedones and inflammatory acne lesions
	CQ42	Is laser treatment effective for acne and acne scars?	C2	Laser treatment may be used to treat acne and acne scars when good results can be expected with an understanding of the features of the various laser treatment machines. However; considering equipment issues, a lack of review in Japan, and a lack of cover by health insurance in Japan, we do not recommend it
Skincare and related treatments				
	CQ43	Is washing one's face effective for acne?	C1	We recommend acne patients to wash their face twice a day as an alternative
	CQ44	Is the use of skincare products for acne effective for acne patient?	C1	We recommend acne patients to use the skincare products for acne as an alternative. However, they should carefully choose low-irritant and non-comedogenic products based on clinical trials in acne patients
	CQ45	Is makeup advice effective for acne?	C1	We recommend providing makeup advice to female acne patients for the purpose of improving QOL as an alternative. However, they should be careful to choose makeup products that are low-irritant and non-comedogenic
	CQ46	Is it effective to generally limit certain foods for acne patients?	C2	We do not recommend generally limiting certain foods for acne patients. When it comes to dietary advice to individual patients, we must sufficiently examine the relationship between the certain foods consumption and acne development
	CQ47	Is dietary advice effective for acne patients?	C2	We currently do not recommend specific dietary advice for acne patients
Rosacea				
Topical treatments	CQ1	Are topical drugs effective for rosacea?	C2	Topical metronidazole and azelaic acid may be used to treat papulopustular rosacea, but we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan, and care should be taken to consider base and concentration
Oral treatments	CQ2	Are oral drugs effective for rosacea?	C2	Oral doxycycline, minocycline and tetracycline may be used to treat papulopustular rosacea, but we do not recommend them. We currently do not recommend *Kampo* or oral ivermectin and metronidazole in the case of demodicosis
Treatments	CQ3	Are laser treatment and phototherapy effective for rosacea?	C2	Pulsed-dye laser (595 nm), neodymium:yttrium–aluminum–garnet laser (1.064 nm) and intense pulsed light may be used to treat erythematotelangiectatic rosacea, but we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan, and sufficient informed consent is required regarding the risk of relapse
Skincare	CQ4	Is skincare effective for rosacea?	C1	We recommend advice on appropriate ultraviolet light protection as well as the use of low-irritant facial cleansers and moisturizers as an alternative to treat rosacea



*This guideline does not cover acne conglobata, acne fulminans, SAPHO syndrome, PAPA syndrome, or similar conditions. Regarding topical drugs in the acute inflammatory phase: fixed combination and combined-use therapies were superior to monotherapy since they have more pharmacological actions. Of the two, fixed combination were placed at the top in the aspect of compliance. The committee did not evaluate the relative superiority between two fixed-dose combination drug.

Notes
1) Glycolic acid, salicylic acid in macrogol
2) Keigairengyoto and Seijobofuto, Jumihaidokuto
3) Ascorbyl tetrahexyldecanoate, sodium L-Ascorbic acid 2-phosphate
4) Injections into inflammatory cysts
5) Keigairengyoto
6) Local injections for treating hypertrophic scars and keloids
7) Makeup advice for the purpose of improving QOL

Abbreviations
AZA : Azelaic acid
BPO : Benzoyl peroxide
CLDM : Clindamycin
NSAID : Non-steroidal anti-inflammatory drug
A/B : Fixed combination of A and B (e.g., CLDM/BPO: fixed combination of clindamycin and benzoyl peroxide)
A+B : Combined use of A together with B (e.g., adapalene + Topical antimicrobial : combined use of adapalene together with topical antimicrobial)

Figure 1. Treatment algorithm for acne vulgaris 2017*.

Table 2. Composition, roles and extent of evidence-gathering responsibilities of the Guidelines for the Treatment of Acne Vulgaris Revision Committee

Roles	Name (practitioner)	CQ evidence gathered
Chairman	Nobukazu Hayashi	CQ4, 9, 10, 13, 14, 15, 19, 26, 28, 31, 38, 39
Supervisory committee members	Keiji Iwatsuki Makoto Kawashima Fukumi Furukawa Yoshiki Miyachi	
Committee members	Hirohiko Akamatsu	CQ30, 32, 34, 36, 37, 40, 41
	Ichiro Kurokawa	CQ1, 6, 21, 22
	Takeshi Kono	CQ12, 23
	Miwa Kobayashi	CQ43, 44, 45, 46, 47
	Miki Tanioka	CQ2, 3, 5, 7, 8, 18, 20, 27, 29
	Minao Furumura	CQ17, 42
	Osamu Yamasaki	CQ11, 25, 35
	Kenshi Yamasaki (Ryoko Shimada-Omori)	CQ1, S2, S3, S4
	Yuki Yamamoto (Chikako Kaminaka)	CQ16, 24, 33

significantly reduce the number of comedones as well as inflammatory and other acne lesions more effectively than the topical application of CLDM1% gel twice a day.[4] Applying CLDM1%/BPO3% once a day had adverse reactions in 24.0% of cases, which was less than the 35.1% of cases that experienced adverse reactions when applying it twice a day.[4]

Based on the above information, we strongly recommend the topical application of CLDM1%/BPO3% once a day to treat inflammatory acne lesions (moderate to severe).

Moreover, although a variety of combination drugs of CLDM and BPO with different concentrations are reported internationally, CLDM1%/BPO3% is the only available in Japan, which is why we did not refer to published work on other concentrations. Furthermore, because there is currently no evidence on long-term maintenance therapy using CLDM1%/BPO3%, we do not recommend the long-term, continuous use of topical CLDM due to the risk of *P. acnes* acquiring resistance to antimicrobials.

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CQ2: Is fixed-dose combination gel of adapalene 0.1% and BPO 2.5% effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend fixed-dose combination gel of adapalene 0.1% and BPO 2.5% to treat inflammatory acne lesions (moderate to very severe).

Comments: Adapalene has an anti-inflammatory effect. BPO also has a direct antibacterial effect due to its oxidant properties. A complementary effect can therefore be expected from their combined use. These guidelines strongly recommend the individual use of both adapalene 0.1% gel and BPO 2.5% gel to treat comedones and inflammatory acne lesions.

Overseas clinical trials have demonstrated that the combination of these drugs is more effective for inflammatory acne lesions than either drug by itself, after conducting RCT involving acne patients with 20–50 facial inflammatory acne lesions.[5,6] However, it is also known that the frequency of skin irritation is higher at the site of drug application.[5,6] A Japanese RCT[7] studying this combination drug involved acne patients with 12–100 facial inflammatory acne lesions and showed significant improvement compared with adapalene 0.1% gel from the first week during a continuous 12-week period. It was not, however, found to be more effective than BPO 2.5% gel. The combination drug was also shown to cause more frequent skin irritation than the individual drugs in the Japanese study.[7] As such, the instructions recommend considering the use of the individual drugs for treatment, before the combination drug.

Based on the above, we strongly recommend fixed-dose combination gel of adapalene 0.1% and BPO 2.5% to treat inflammatory acne lesions (moderate to very severe).

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CQ3: Is the combined use of adapalene 0.1% gel together with a topical antimicrobial effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend the combined use of adapalene 0.1% gel together with a topical antimicrobial to treat inflammatory acne lesions (mild to severe).

Comments: As retinoids improve comedones and have an anti-inflammatory effect, and antimicrobials have additional

anti-inflammatory properties, it is expected that their combined use will be quicker and more effective in improving both comedones and inflammatory acne lesions.

According to an RCT comparing the combined use of adapalene 0.1% gel together with CLDM 1% lotion and the individual use of CLDM 1% lotion, on acne patients with mild to moderate inflammatory acne lesions,[8] the effectiveness of the two treatments diverges in the 4th week. The reduction rates for comedones and inflammatory acne lesions in the 12th week were 42.5% and 55.0% for combined use, compared with 16.3% and 44.2% for individual use, respectively. A similar Japanese RCT compared combined therapies using adapalene 0.1% gel together with CLDM 1% gel, nadifloxacin (NDFX) 1% cream or 1% lotion on acne vulgaris patients with mild to moderate or moderate to severe inflammatory acne lesions. As for the data from the overseas study, it was found that 12 weeks of combination therapy was effective.[9–12]

Based on the above information, we strongly recommend the combined use of adapalene 0.1% gel together with topical antimicrobials to treat inflammatory acne lesions (mild to severe).

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CQ4: Is BPO 2.5% gel effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend BPO 2.5% gel to treat inflammatory acne lesions (mild to moderate).

Comments: As BPO is a strong oxidant, it easily breaks up into free radicals and is thought to improve inflammatory acne lesions by antibacterial effect toward *P. acnes*. BPO is considered not to create resistant bacteria, as no bacteria resistant to this drug have been found to date.

A Japanese RCT, studying acne vulgaris patients with 11–40 facial inflammatory acne lesions over a 3-month period, has shown that BPO 2.5% gel can reduce inflammatory acne lesions by 72.7%, which is significantly more effective than the 41.7% reduction for the placebo. Adverse events included erythema and peeling skin where applied, but these were within tolerable limits.[13]

According to studies[14] comparing the efficacy of BPO 10%, 5% and 2.5% and past published work reviews,[15] there is little difference in efficacy if the concentration is at least 2.5% and adverse events intensify at 10%.[14] As such, a concentration of 5% or less is advisable. BPO 3% gel yielded good results in a Japanese RCT[16] involving acne vulgaris patients with 17–60 inflammatory acne lesions, but there are currently no plans to develop a BPO 3% drug.

Based on the above, we strongly recommend topical BPO 2.5% gel to treat inflammatory acne lesions (mild to moderate).

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CQ5: Is adapalene 0.1% gel effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend adapalene 0.1% gel to treat inflammatory acne lesions (mild to severe).

Comments: Adapalene is a drug that is highly effective for improving comedones, normalizing keratinization in the follicular epithelium and preventing the formation of new comedones. As such, it also prevents the inflammatory acne lesions that appear after comedones. Adapalene is also known to have a direct anti-inflammatory effect.

Several overseas RCT have shown that topical therapy using adapalene 0.1% gel reduces inflammatory acne lesions. According to a meta-analysis[17] that summarizes five RCT, treatment using topical adapalene 0.1% gel over 12 weeks reduced inflammatory acne lesions by 52.3%. In the overseas studies, approximately 80% of patients suffered adverse events such as desquamation, erythema and skin dryness, and approximately 20% experienced burning sensation and itching; however, the majority of cases were mild and almost none warranted discontinued use. Moreover, RCT[18,19] involving Japanese acne vulgaris patients with 10–100 inflammatory acne lesions showed similar effects and adverse events for topical adapalene 0.1% to the overseas reports.

Based on the above, we strongly recommend topical adapalene 0.1% gel to treat inflammatory acne lesions (mild to severe).

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CQ6: Are topical antimicrobials effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend topical antimicrobials (CLDM, NDFX and ozenoxacin) to treat inflammatory acne lesions.

Comments: Eleven high-quality LII RCT[20–30] on the effectiveness of topical drugs with CLDM for inflammatory acne lesions have been reported overseas. These involved patients with inflammatory acne lesions (moderate to severe), treated over 8–12 weeks. Most of these studies examined topical CLDM 1% with gel or lotion bases, applied twice a day. The number of cases ranged 46–1026 and patient ages ranged 12–35 years. Efficacy was determined based on number of acne lesions (10/11 cases) and general improvement (4/11 cases). All studies compared topical CLDM with placebo, and showed that the former was significantly more effective in reducing inflammatory acne lesions (papules and pustules). Adverse reactions included dryness, peeling, burning sensation and itching; however, all were mild.

In Japan, four LII RCT[31–34] and three LIV non-randomized studies on the effectiveness of CLDM were reported, studying acne vulgaris patients with at least 10 inflammatory acne lesions (moderate or more severe), using the number of acne lesions and general improvement as indices. All of these studies showed good results. Reported adverse reactions include irritation, itching, dryness and stinging where applied;[31–34] however, these were mild.

Moreover, two high-quality LII RCT on NDFX 1% cream have been reported overseas.[35,36] These studies targeted mild to moderate acne, had treatment periods of 8[36] and 12 weeks,[35] respectively, included 37[36] and 474 cases,[35] respectively, applied the cream twice a day and evaluated effectiveness based on the number of acne lesions.[35–37] These two RCT showed a significant reduction in the number of inflammatory acne lesions. Adverse reactions included itching, erythema, dryness, peeling, burning sensation and skin tightness at a frequency of 3–15%; however, these were mild.[24]

In Japan, three LII RCT[37–39] and seven non-randomized studies on the effectiveness of NDFX for inflammatory acne lesions have been reported, each showing good results. Reported adverse reactions include erythema, dryness, burning sensation, irritation, itching and stinging where applied; however, these were mild.

Two LII RCT[40,41] on the effectiveness of ozenoxacin lotion for inflammatory acne lesions have been reported, showing its usefulness. Adverse reactions include mild dryness and desquamation where applied in only approximately 3% of cases.[40]

Based on the above, we strongly recommend topical antimicrobials (CLDM, NDFX, ozenoxacin) to treat inflammatory acne lesions.

Regarding other topical antimicrobial therapies, tetracycline and erythromycin have also been reported to be effective in RCT. Other topical antimicrobials include chloramphenicol, oxytetracycline, gentamycin, baramycin, fradiomycin and sodium fusidate, but these cannot be used to treat acne in Japan as they are not covered by health insurance in Japan. The dosage forms also have not been sufficiently examined in Japan. As such, this strength of recommendation only applies to CLDM, NDFX and ozenoxacin.

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CQ7: Is the combined use of fixed-dose combination gel containing adapalene 0.1% and BPO 2.5% together with an oral antimicrobial effective for inflammatory acne lesions?

Promotion score: A.

Recommendation: We strongly recommend the combined use of fixed-dose combination gel containing adapalene 0.1% and BPO 2.5% together with an oral antimicrobial to treat inflammatory acne lesions (moderate to very severe).

Comments: These guidelines strongly promote the individual use of adapalene, BPO and oral antimicrobials to treat inflammatory acne lesions. Moreover, their functional mechanisms differ. As such, combined treatment using these three drugs is an alternative to treat the very severe cases.

No RCT on these three drugs have been carried out in Japan. However, overseas RCT involving acne patients (moderate to very severe) with at least 20 facial inflammatory acne lesions have compared oral antimicrobials with the combined use of oral antimicrobials and fixed-dose combination drugs containing adapalene and BPO.[42,43] The oral antimicrobials used were doxycycline (100 mg/day) and lymecycline (300 mg/day). Both studies showed that combined use of these drugs was significantly more effective for improving non-inflammatory acne lesions from the 2nd week. Similarly, combined used was also shown to be significantly more effective than individual therapy for improving inflammatory acne lesions from the 2nd to 4th week. This difference was maintained for 12 weeks and grew.

Based on the above, we strongly recommend the combined use of fixed-dose combination gel of adapalene 0.1% and BPO 2.5% together with oral antimicrobials to treat inflammatory acne lesions (moderate to very severe).

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CQ8: Is the combined use of adapalene 0.1% gel together with an oral antimicrobial effective for inflammatory acne lesions?

Strength of recommendation: A.

Recommendation: We strongly recommend the combined use of adapalene 0.1% gel together with an oral antimicrobial to treat inflammatory acne lesions (moderate to very severe).

Comments: Because retinoids improve comedones and have an anti-inflammatory effect, and antimicrobials have both antibacterial and anti-inflammatory effects, it is expected that their combined use will improve both comedones and inflammatory acne lesions.

According to an RCT[44] involving acne patients with moderate to severe inflammatory acne lesions, comparing patients treated with the combined use of adapalene 0.1% gel and 300 mg oral lymecycline and patients treated with only 300 mg oral lymecycline, combined use was shown to be quicker and more effective. By the 12th week, combined use reduced comedones and inflammatory acne lesions by 56.6% and 60.3%, while the individual drug reduced these conditions by 47.6% and 45.6%, respectively. Similar results have been obtained from an RCT[45] comparing the combined use of topical adapalene 0.1% gel together with oral 100 mg doxycycline and the individual use of oral 100 mg doxycycline.

Moreover, a Japanese RCT compared a group treated with combined use of adapalene 0.1% gel together with faropenem (600 mg/day) for 4 weeks, a group treated with the combined use of adapalene together with faropenem (600 mg/day) for 2 weeks and a group treated with only topical adapalene 0.1% gel. Combined use of adapalene 0.1% gel together with oral faropenem (600 mg/day) for 4 weeks improved inflammatory acne lesions quicker and more effectively.[46]

Based on the above, we strongly recommend the combined use of adapalene 0.1% gel together with oral antimicrobials to treat inflammatory acne lesions (moderate to severe).

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46 Hayashi N, Kawashima M. Multicenter randomized controlled trial on combination therapy with adapalene 0.1% gel and oral antibiotics for acne vulgaris: comparison of the efficacy of adapalene gel alone and in combination with oral faropenem. *J Dermatol* 2012; **39**: 511–515. (evidence level II)

CQ9: Are topical non-steroidal anti-inflammatory drugs (NSAIDs) effective for inflammatory acne lesions?

Strength of recommendation: C1.

Recommendation: We recommend ibuprofen piconol cream as an alternative to treat inflammatory acne lesions (mild to moderate).

Comments: Two Japanese RCT[47,48] were carried out on the hypothesis that NSAIDs have usefulness for acne inflammation, examining the usefulness of topical NSAIDs for inflammatory acne lesions. One[47] is highly reliable as it was a double-blind RCT involving a relatively large pool of 110 cases. In this study, ibuprofen cream and placebo were compared, with a significant difference in general improvement confirmed after the 3rd week. After the 4th week, the usefulness in the ibuprofen group was 66%, and the usefulness in the placebo group 33%, showing the higher effectiveness of the drug. An open comparative study of the topical ibuprofen cream and NDFX cream has been reported,[49] but this trial was non-randomized and non-blinded, and included cases of combined use of oral antimicrobials. We cannot argue for the effectiveness of ibuprofen piconol and NDFX based on this report. We recommend these drugs to treat acne because RCT have been conducted, but the strength of recommendation is C1 due to the lack of any comparison with topical antimicrobials.

Based on the above, we recommend ibuprofen piconol cream as an alternative to treat acne (mild to moderate inflammatory acne lesions).

REFERENCES

47 Acne Research Team. Studies on clinical effects of ibuprofen piconol cream, a non-steroidal external drug on acne vulgaris double blind arials. *Clinical Report* 1985; **19**: 1807–1814. (in Japanese). (evidence level II)

48 Hayakawa R, Matsunaga K, Ninagawa Y. Studies on clinical effects of ibuprofen piconol cream for acne vulgaris patients. *Nishinihon J Dermatol* 1985; **47**: 899–908. (in Japanese). (evidence level II)

49 Deguchi H. Comparison of the treatment effects of topical nonsteroidal drugs (ibuprofen piconol cream) and topical antibacterial drugs (nadifloxacin cream) on facial acne vulgaris patients. *Iyaku no mon* 2001; **41**: 578–582. (in Japanese). (evidence level VI)

CQ10: Are topical steroids effective for inflammatory acne lesions?

Strength of recommendation: C2.

Recommendation: We do not recommend topical steroids to treat inflammatory acne lesions.

Comments: According to overseas RCT[50–52] that have tested topical steroids on acne, there are no statistically significant differences between topical steroids and placebo, and there is no evidence of improvement of inflammatory lesions due to topical steroids. As such, there is no reason to assume that topical steroids are effective treatments for acne. Topical steroids can be expected to temporarily stop inflammation, but it is also well-known that they induce acne. Long-term use of topical steroids is clearly unadvisable when taking into consideration their various adverse events. Until sufficient evidence is gathered about the effects of short-term use, we do not recommend this either.

Based on the above, we do not recommend topical steroids to treat inflammatory acne lesions.

REFERENCES

50 Hull SM, Cunliffe WJ. The use of a corticosteroid cream for immediate reduction in the clinical signs of acne vulgaris. *Acta Derm Venereol* 1989; **69**: 452–453. (evidence level II)

51 Wexler L. Two controlled studies of a topical steroid preparation in the treatment of acne vulgaris. *Appl Ther* 1968; **10**: 455–457. (evidence level II)

52 Guerrier CJ, Thornton EJ. Double-blind comparison of two similar lotion formulations, one without and the other with hydrocortisone acetate ('Actinac') in the treatment of acne vulgaris. *Curr Med Res Opin* 1980; **6**: 377–379. (evidence level II)

CQ11: Are oral antimicrobials effective for inflammatory acne lesions?

Strength of recommendation: A (doxycycline), A* (minocycline), B (roxithromycin, faropenem) or C1 (tetracycline, erythromycin, clarithromycin, levofloxacin, tosufloxacin, ciprofloxacin, lomefloxacin, cefuroxime axetil).

Recommendation: We strongly recommend oral antimicrobials to treat inflammatory acne lesions.

Comments: *P. acnes* plays an important role in acne inflammation. Although susceptibility is a critical factor to decide antimicrobial in general infections, tetracyclines and macrolides are often prescribed not only for antibacterial effect, but also for an anti-inflammatory effect in treating acne. Several RCT on the effects of tetracyclines and

macrolides on acne have been reported. Most of them involving 15–35-year-old acne patients with mild to severe inflammatory acne. Various control drugs were used, such as placebo, topical antimicrobials and tetracyclines, whose effectiveness had already been demonstrated. Drugs were evaluated based on the reduction rate of acne lesions and general improvement.

For tetracyclines, there were five RCT for doxycycline, four RCT for tetracycline and a systematic review of minocycline. For macrolides, there were three RCT for roxithromycin and two RCT for erythromycin. For penem, there were two RCT for faropenem. Doxycycline sustained-release drugs and azithromycin pulse therapy are not approved in Japan and trimethoprim is not used to treat acne in Japan, which is why these three treatments were not included in these guidelines.

As their efficacy has been shown in many RCT, we strongly recommend oral antimicrobials for the treatment of inflammatory acne lesions, but long-term use of antimicrobials should be avoided due to the risk of resistant bacteria. The Global Alliance recommends to limit the administration period of antimicrobials to no more than 3 months and to reevaluate continuation after 6–8 weeks of use.[53] Moreover, we recommend combined use together with BPO or adapalene followed by maintenance therapy, avoiding the use of oral antimicrobials as monotherapy and combined use together with topical antimicrobials.[53,54]

The strengths of recommendation for each antimicrobial were decided after taking into consideration the respective evidence levels, how the drug is used in Japan and whether it has been approved for acne treatment.

REFERENCES

53 Thiboutot D, Gollnick H, Bettoli V *et al.* Global alliance to improve outcomes in acne. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol* 2009; **60**: S1–S50. (evidence level VI)

54 Nast A, Dréno B, Bettoli V *et al.* European evidence-based (S3) guidelines for the treatment of acne. *J Eur Acad Dermatol Venereol* 2012; **26**(Suppl 1): 1–29. (evidence level VI)

Doxycycline

Strength of recommendation: A.

Recommendation: We strongly recommend oral doxycycline to treat inflammatory acne lesions.

Comments: Doxycycline is one of the tetracyclines that can be expected to have antibacterial and anti-inflammatory effects. The effectiveness of doxycycline has been shown in an RCT[55] where 100 mg doxycycline and placebo were administrated for 4 weeks, and were also administrated in a cross-over trial to compare the two. An RCT comparing 50 mg doxycycline and 100 mg minocycline has similarly shown the equivalence of minocycline.[56] Moreover, comparative studies with adapalene, BPO and oral antimicrobials have been using doxycycline as a control drug in recent years. Adverse events include hyper-photosensitivity,[54] but this recedes after stopping treatment. Other adverse events are mild stomachache and headache, so European guidelines[54] recommend doxycycline over minocycline.

Based on the above, we strongly recommend doxycycline to treat inflammatory acne lesions.

REFERENCES

55 Plewig G, Petrozzi JW, Berendes U. Double-blind study of doxycycline in acne vulgaris. *Arch Dermatol* 1970; **101**: 435–438. (evidence level II)

56 Harrison PV. A comparison of doxycycline and minocycline in the treatment of acne vulgaris. *Clin Exp Dermatol* 1988; **13**: 242–244. (evidence level II)

Minocycline

Strength of recommendation: A*.

Recommendation: We recommend oral minocycline to treat inflammatory acne lesions.

Comments: Minocycline not only has an antibacterial effect, but is also known to suppress lipase activity, leukocyte migration and reactive oxygen species (ROS). Minocycline is recommended on the basis of a systematic review[57] of 39 RCT. There have been RCT involving placebo, tetracycline, doxycycline, topical CLDM, topical erythromycin, isotretinoin and other drugs. It is certain that minocycline is effective for acne, but compared to equally-effective doxycycline, it comes with a high frequency of adverse events, such as dizziness and pigmentation, as well as serious adverse events, such as autoimmune disease and drug-induced hypersensitivity syndrome, which urges caution.[57,58] Some overseas guidelines also judge minocycline to be inferior to doxycycline due to the adverse events, despite evidence of their comparability.[54] Having taken adverse events into consideration, the committee decided to strongly recommend doxycycline while giving minocycline a strength of recommendation of A*.

Based on the above, we recommend oral minocycline to treat inflammatory acne lesions.

REFERENCES

57 Garner SE, Eady A, Bennett C, Newton JN, Thomas K, Popescu CM. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database Syst Rev*, 2012; **8**: CD002086. (evidence level I)

58 Lebrun-Vignes B, Kreft-Jais C, Castot A, Chosidow O. French Network of Regional Centers of Pharmacovigilance: comparative analysis of adverse drug reactions to tetracyclines: results of a French national survey and review of the literature. *Br J Dermatol* 2012; **166**: 1333–1341.

Roxithromycin

Strength of recommendation: B.

Recommendation: We recommend oral roxithromycin to treat inflammatory acne lesions.

Comments: Roxithromycin is a semi-synthetic 14-membered ring macrolide which has improved absorption and pharmacokinetics when compared with erythromycin. It is approved for use for acne (inflammatory acne lesions). One RCT[59] has shown its effectiveness in comparison with roxithromycin and placebo. Two RCT[60,61] showed no significant difference in the reduction of inflammatory acne lesions when compared with minocycline and faropenem. The latter was conducted in Japan. All reports indicated only mild adverse events.

Based on the above, we recommend oral roxithromycin to treat inflammatory acne lesions.

REFERENCES

59 Ferahbas A, Utas S, Aykol D, Borlu M, Uksal U. Clinical evaluation of roxithromycin: a double-blind, placebo-controlled and crossover trial in patients with acne vulgaris. *J Dermatol* 2004; **31**: 6–9. (evidence level II)

60 Hashimoto A, Tsuboi H, Hiramatsu M, Sekine A, Komemoto K, Nishiyama S. The availability of roxithromycin (Rulid) for the acne. comparison examination with minocycline, *Nishinihon*. *J Dermatol* 1996; **58**: 135–137. (in Japanese). (evidence level II)

61 Hayashi N, Kawashima M. Efficacy of oral antibiotics on acne vulgaris and their effects on quality of life: a multicenter randomized controlled trial using minocycline, roxithromycin and faropenem. *J Dermatol* 2011; **38**: 111–119. (evidence level II)

Faropenem

Strength of recommendation: B.

Recommendation: We recommend oral faropenem to treat inflammatory acne lesions.

Comments: Faropenem is a penem that is approved for inflammatory acne.

An RCT treated patient groups with one of the oral drugs minocycline, roxithromycin or faropenem over 4 weeks. This study found each group had a significant reduction in inflammatory acne lesions compared with when treatment began, with no significant difference between the three groups.[62] Another RCT[63] testing the combined use of adapalene 0.1% gel together with faropenem found this treatment to be more effective than adapalene 0.1% gel by itself. Two before-and-after clinical studies have also been conducted.[64,65]

Based on the above, we recommend oral faropenem to treat inflammatory acne lesions.

REFERENCES

62 Hayashi N, Kawashima M. Efficacy of oral antibiotics on acne vulgaris and their effects on quality of life: a multicenter randomized controlled trial using minocycline, roxithromycin and faropenem. *J Dermatol* 2011; **38**: 111–119. (evidence level II)

63 Hayashi N, Kawashima M. Multicenter randomized controlled trial on combination therapy with adapalene 0.1% gel and oral antibiotics for acne vulgaris: comparison of the efficacy of adapalene gel alone and in combination with oral faropenem. *J Dermatol* 2012; **39**: 511–515. (evidence level II)

64 Nogita T. Combination therapy with faropenem and adapalene gel 0.1% for acne vulgaris with lnflammatory lesions. *J New Rem Clin*, 2010; **59**: 392–404. (in Japanese) (evidence level III)

65 Toda K, Shimonaka M, Matsushima S, Nishiwaki F, Yokota H. Clinical efficacy of faropenem sodium (FRPM) in the treatment of acne vulgaris. *J New Rem Clin* 2006; **55**: 1439–1445. (in Japanese). (evidence level IV)

Tetracycline

Strength of recommendation: C1.

Recommendation: We recommend oral tetracycline as an alternative to treat inflammatory acne lesions.

Comments: Tetracycline can be expected to have a similar anti-inflammatory effect as minocycline. Many RCT of tetracycline have been conducted; however, the majority were comparative studies for demonstrating the effectiveness of topical drugs and combined therapies. RCT comparing oral tetracycline with topical BPO,[66] topical CLDM[67–70] and topical tetracycline[70,71] all showed that oral tetracycline by itself is more effective than placebo, alternatively showing its effectiveness through before-and-after comparisons. Even so, results indicate that its effectiveness is equivalent or inferior to that of the topical drug. Moreover, while the population was small, one RCT[72] also showed that the effect of tetracycline was not significantly different from placebo.

Based on the above, we recommend oral tetracycline as an alternative to treat inflammatory acne lesions.

REFERENCES

66 Ozolins M, Eady EA, Avery AJ *et al.* Comparison of five antimicrobial regimens for treatment of mild to moderate inflammatory facial acne vulgaris in the community: randomized controlled trial. *Lancet* 2004; **364**: 2188–2195. (evidence level II)

67 Katsambas A, Towarky AA, Stratigos J. Topical clindamycin phosphate compared with oral tetracycline in the treatment of acne vulgaris. *Br J Dermatol* 1987; **116**: 387–391. (evidence level II)

68 Gratton D, Raymond GP, Guertin-Larochelle S *et al.* Topical clindamycin versus systemic tetracycline in the treatment of acne. *J Am Acad Dermatol* 1982; **7**: 50–53. (evidence level II)

69 Braathen LR. Topical clindamycin versus oral tetracycline and placebo in acne vulgaris. *Scan J Infect Dis Suppl* 1984; **43**: 71–75. (evidence level II)

70 Burton J. A placebo-controlled study to evaluate the efficacy of topical tetracycline and oral tetracycline in the treatment of mild to moderate acne. Dermatology Research Group. *J Int Med Res* 1990; **18**: 94–103. (evidence level II)

71 Blaney DJ, Cook CH. Topical use of tetracycline in the treatment of acne: a double-blind study comparing topical and oral tetracycline therapy and placebo. *Arch Dermatol* 1976; **112**: 971–973. (evidence level II)

72 Wong RC, Kang S, Heezen JL, Voorhees JJ, Ellis CN. Oral ibuprofen and tetracycline for the treatment of acne vulgaris. *J Am Acad Dermatol* 1984; **11**: 1076–1081. (evidence level II)

Erythromycin

Strength of recommendation: C1.

Recommendation: We recommend oral erythromycin as an alternative to treat inflammatory acne lesions.

Comments: Erythromycin can be expected to be effective for acne because of its strong antibacterial effects and ability to reduce lipases and fatty acids in *P. acnes*. However, in an RCT[73] testing tetracycline on 200 cases of moderate to severe inflammatory acne lesions, erythromycin has so far been found only to have an improvement rate of 77%, compared with the 89% of tetracycline, so the evidence is not yet sufficient. Adverse events of erythromycin include gastrointestinal disorders such as nausea and diarrhea in 7% of cases. Other guidelines also mentioned the risk of resistant bacteria during treatment.[74]

Based on the above, we recommend erythromycin as an alternative to treat inflammatory acne lesions.

REFERENCES

73 Gammon WR, Meyer C, Latis S, Shenefelt P, Reizner G, Cripps DJ. Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris. *J Am Acad Dermatol* 1986; **14**: 183–186. (evidence level II)

74 Strauss JS, Krowchuk DP, Leyden JJ *et al.* Guideline of care for acne vulgaris management. *J Am Acad Dermatol* 2007; **56**: 651–663. (evidence level VI)

Clarithromycin

Strength of recommendation: C1.

Recommendation: We recommend oral clarithromycin as an alternative to treat inflammatory acne lesions.

Comments: Like roxithromycin, clarithromycin is a derivative of erythromycin that does not upset the gastric acid, is easily absorbed through the alimentary canal and has a long half-life in blood. While not an RCT, it has been reported[75] that 4 weeks of clarithromycin administration to 45 patients with moderate or less severe inflammatory acne resulted in general improvement of 57.8% (200 mg/day) and 79.2% (400 mg/day).

Based on the above, we recommend clarithromycin as an alternative to treat inflammatory acne lesions.

REFERENCE

75 Ishikawa O, Miyachi Y, Kudo T *et al.* Clinical usefulness of clarithromycin (Klaricid tablets) for inflammatory acne. *Acta Dermatol (Kyoto)* 1996; **91**: 403–407. (in Japanese). (evidence level III)

Levofloxacin

Strength of recommendation: C1.

Recommendation: We recommend oral levofloxacin as an alternative to treat inflammatory acne lesions.

Comments: Levofloxacin is approved for use for inflammatory acne. Two Japanese before-and-after clinical studies[76,77] have shown that this drug reduces inflammatory acne lesions, demonstrating its effectiveness.

Based on the above, we recommend levofloxacin as an alternative to treat inflammatory acne lesions.

REFERENCES

76 Kawada A, Aragane Y, Tezuka T. Levofloxacin is effective for inflammatory acne and achieves high levels in the lesions: an open study. *Dermatology* 2001; **204**: 301–302. (evidence level III)

77 Kawada A, Wada T, Oiso N. Clinical effectiveness of once-daily levofloxacin for inflammatory acne with high concentrations in the lesions. *J Dermatol* 2012; **39**: 94–96. (evidence level III)

Tosufloxacin

Strength of recommendation: C1.

Recommendation: We recommend oral tosufloxacin as an alternative to treat inflammatory acne lesions.

Comments: One Japanese report[78] states that when administrated to 20 cases of acne pustulosa, cystic acne and acne conglobata, tosufloxacin had a bacteria elimination rate of 93.1%, an effectivity rate of 75% and a usefulness rate of 70%, with no adverse events. Health insurance in Japan covers its use for treating acne (inflammatory acne lesions).

Based on the above, we recommend tosufloxacin as an alternative to treat inflammatory acne lesions.

REFERENCE

78 Matsumoto T. Clinical effects for acne pustulosa, cystic acne, and acne conglobata of tosyl acid tosufloxacin tablets. *Nishinihon J Dermatol*, 1995; **57**: 375–378. (in Japanese) (evidence level IV)

Ciprofloxacin

Strength of recommendation: C1.

Recommendation: We recommend oral ciprofloxacin as an alternative to treat inflammatory acne lesions.

Comments: A comparison involving minocycline treatment of 54 cases of acne pustulosa patients showed effectivity rates to be 66% in the ciprofloxacin group and 68% in the minocycline group.[79] Three out of 40 cases in the ciprofloxacin group experienced adverse events (one case of nausea, two cases of diarrhea), while two out of 35 cases in the minocycline group experienced adverse events (one case of headache, one case of leukopenia and hematocrit reduction).

Based on the above, we recommend ciprofloxacin as an alternative to treat inflammatory acne lesions.

REFERENCE

79 Tsuboi R, Koike M, Takimoto R, Nishimura K, Manabe M, Ogawa H. Study on the Efficacy and Safety of ciprofloxacin (CPFX) versus minocycline (MINO) for the treatment of acne pustulosa. *Antibiot Chemother* 1999; **15**: 909–916. (in Japanese). (evidence level III)

Lomefloxacin

Strength of recommendation: C1.

Recommendation: We recommend oral lomefloxacin as an alternative to treat inflammatory acne lesions.

Comments: In Japan, one before-and-after clinical study[80] has been reported. Twenty patients with inflammatory acne were administrated lomefloxacin, upon which acne lesions were reduced significantly and no adverse events were observed.

Based on the above, we recommend lomefloxacin as an alternative to treat inflammatory acne lesions.

REFERENCE

80 Hayakawa R. Clinical evaluation of lomefloxacin (Lomebact) on acne vulgaris (Pustular type). *Antibiot Chemother* 1992; **8**: 1380–1387. (in Japanese). (evidence level IV)

Cefuroxime axetil

Strength of recommendation: C1.

Recommendation: We recommend oral cefuroxime axetil as an alternative to treat inflammatory acne lesions.

Comments: Cefuroxime axetil is antimicrobial belonging to the cephem. One study[81] has compared the number of acne lesions before and after administration in pustular acne patients. This drug is approved for inflammatory acne.

Based on the above, we recommend cefuroxime axetil as an alternative to treat inflammatory acne lesions.

REFERENCE

81 Hayakawa R, Matsunaga K, Suzuki M, Ogino Y. Clinical evaluation of cefuroxime axetil (CXM-AX) on acne pustulosa. *Skin Res* 1989; **31**: 591–600. (in Japanese). (evidence level III)

CQ12: Is *Kampo* effective for inflammatory acne lesions?

Strength of recommendation: C1 (*Keigairengyoto*, *Seijobofuto*, *Jumihaidokuto*) and C2 (*Orengedokuto*, *Unseiin*, *Unkeito*, *Keishibukuryogan*)

Recommendation: We recommend *Keigairengyoto*, *Seijobofuto* and *Jumihaidokuto* as alternatives to treat inflammatory acne lesions if other treatments are ineffective or cannot be implemented. *Orengedokuto*, *Unseiin*, *Unkeito* and *Keishibukuryogan* may be used, but we do not recommend them.

Comments: There is LIII and LV evidence showing the effectiveness of *Orengedokuto*,[82,85,86] *Jumihaidokuto*,[82,85,86] *Keigairengyoto*[83,85] and *Seijobofuto*[83,85] on acne inflammatory acne lesions. There is LV evidence showing the effectiveness of *Unseiin*, *Unkeito*[86] and *Keishibukuryogan*[85,87–89] (all the above are extract preparations of crude drugs).[82–89] However, these evaluations are not confirmed at present, because some of these studies included combined use with antimicrobials. Moreover, we cannot evaluate decoction, the extraction of water-soluble drug substances by boiling, due to a severe lack of evidence. Even so, when considering that adverse events are minimal, the above *Kampo* extracts can be used as an alternative if other treatments are ineffective or cannot be implemented. Acne treatment using *Keigairengyoto* and *Seijobofuto* is covered by health insurance in Japan, while the use of *Jumihaidokuto* is covered when treating pyogenic skin diseases.

Based on the above, we recommend *Keigairengyoto*, *Seijobofuto* and *Jumihaidokuto* as alternatives to treat inflammatory acne lesions if other treatments are ineffective or cannot be implemented. *Orengedokuto*, *Unseiin*, *Unkeito* and *Keishibukuryogan* may be administrated, but we do not recommend them.

REFERENCES

82 Okuma M. Treatment of acne by chinese drugs and external application. *J Trad Med* 1993; **10**: 131–134. (in Japanese). (evidence level III)
83 Hashimoto Y, Matsuo S, Iizuka H. Experiences of using Seijobofuto against acne. *Twelfth Record of the Society of Oriental Medicine (Dermatology)*, 1994: 46–53. (in Japanese) (evidence level III)
84 Horiguchi Y, Matsumoto I, Karasaki K. Therapeutic effect of Sei-jobofu-to extract granules and combination drug therapy on common acne. *Acta Dermatol(Kyoto)*, 1997; **92**: 407–412. (in Japanese) (evidence level III)
85 Takeichi M. Practical administration of Kampo (traditional herbal medicine) against acne. *Sci Kampo Med* 2005; **29**: 282–286. (in Japanese). (evidence level V)
86 Hayashi C. Acne vulgaris treatment in gynecology (first report). *Recent Progress of Kampo Medicine in Obstetrics and Gynecology* 2006; **23**: 132–136. (in Japanese). (evidence level V)
87 Tezuka M. Treatment of acne vulgaris with keishibukuryogan (Gui Zhi Ling Wan) in cases identified as having kitai ketsuo pattern. *J New Rem Clin* 2005; **54**: 907–914. (in Japanese). (evidence level V)
88 Tezuka M. Treatment of acne vulgaris with keishibukuryogan (Gui Zhi Fu Ling Wan) in cases identified as having kitai ketsuo pattern (second report). *J New Rem Clin* 2006; **55**: 278–285. (in Japanese). (evidence level V)
89 Tezuka M. Treatment of acne vulgaris with keishibukuryogan (Gui Zhi Fu Ling Wan) in cases identified as having kitai ketsuo pattern (third report). *J New Rem Clin* 2006; **55**: 538–545. (in Japanese). (evidence level V)

CQ13: Are oral steroids effective for very severe inflammatory acne lesions?

Strength of recommendation: C2.

Recommendation: We do not recommend oral steroids to treat very severe inflammatory acne lesions.

Comments: Some overseas guidelines[90] recommend oral steroids, but there is no evidence showing the clinical effectiveness of p.o. administrated steroids on acne vulgaris. At the same time, acne is a well-known side-effect of oral steroids.

Based on the above, we do not recommend oral steroids to treat very severe inflammatory acne lesions.

REFERENCE

90 Strauss JS, Krowchuk DP, Leyden JJ *et al.* Guidelines of care for acne vulgaris management. *J Am Acad Dermatol* 2007; **56**: 651–663. (evidence level VI)

CQ14: Is oral DDS (diaminodiphenyl sulfone, dapsone) effective for inflammatory acne lesions?

Strength of recommendation: C2.

Recommendation: We do not recommend oral DDS to treat inflammatory acne lesions.

Comments: Kaminsky *et al.*[91] administrated oral DDS to 484 acne patients, reporting that it had no effect on acne patients with papules, pustules and few cysts, although was effective on cystic acne and acne conglobata. There is an old placebo-controlled RCT[92] using DDS but not detailing the acne symptoms. Thus, there are no reports on the effectiveness of DDS to treat acne vulgaris. We do not recommend DDS to treat inflammatory acne lesions.

Meanwhile, a number of case reports indicate that DDS is effective for nodulocystic acne, acne fulminans and acne conglobata that do not respond to antimicrobials. Moreover, a report that identified oral 13-*cis*-retinoic acid as more effective than DDS showed that while the DDS group did not have a significant reduction of acne lesions on the back and chest, facial symptoms did improve when comparing before and after.[93] Furthermore, there are Japanese case-series studies[94,95] on its effectiveness for acne conglobata. One of them reported that five cases out of seven not responding to antimicrobials showed improvement.[94] The effectiveness of DDS for acne fulminans whose symptoms were not improved by retinoic acid was reported.[96] If we take into account that oral retinoic acid for acne is not practised in Japan, it becomes possible to name DDS as an alternative to treat nodulocystic acne, acne fulminans and acne conglobata.

Even so, DDS use to treat acne is not covered by health insurance in Japan, and caution is advised administrating the drug due to the risk of adverse events including a serious drug eruption known as sulfone syndrome, DDS syndrome or drug-induced hypersensitivity syndrome as well as anemia.[97]

Based on the above, we do not recommend DDS to treat inflammatory acne lesions.

REFERENCES

91 Kaminsky CA, de Kaminsky AR, Schicci C, de Morini MV. Acne: treatment with diaminodiphenylsulfone. *Cutis* 1974; **13**: 869–871. (evidence level III)

92 Ross CM. The treatment of acne vulgaris with dapsone. *Br J Dermatol* 1961; **73**: 367–370. (evidence level III)

93 Prendiville JS, Logan RA, Russell-Jones R. A comparison of dapsone with 13-cis retinoic acid in the treatment of nodular cystic acne. *Clin Exp Dermatol* 1988; **13**: 67–71. (evidence level II)

94 Miyachi Y, Yoshioka A, Oguchi M. Anti-oxidant mechanism of action of Dapsone on inflammatory acne. *Acta Dermatol (Kyoto)*, 1985; **80**: 277–281. (in Japanese) (evidence level V)

95 Wakabayashi M, Fujii N, Fujimoto N, Tanaka T. Usefulness of dapsone for the treatment of Asian severe acne. *J Dermatol* 2013; **40**: 502–504. (evidence level V)

96 Tan BB, Lear JT, Smith AG. Acne fulminans and erythema nodosum during isotoretinoin therapy responding to dapsone. *Clin Exp Dermatol* 1997; **22**: 26–27. (evidence level V)

97 Agrawal S, Agarwalla A. Dapsone hypersensitivity syndrome: a clinico-epidemiological review. *J Dermatol* 2005; **32**: 883–889. (evidence level V)

CQ15: Are oral NSAIDs effective for inflammatory acne lesions?

Strength of recommendation: C2.

Recommendation: We do not recommend oral NSAIDs to treat inflammatory acne lesions.

Comments: No clinical studies have been conducted to confirm the effects of oral NSAIDs by themselves on acne. There is one overseas report[98] on the effects of combined use together with antimicrobials, where an RCT involving four test groups (an ibuprofen group, a tetracycline group, a combined-use group and a placebo group) showed the usefulness of combined use of the two drugs. This report showed that both 1000 mg/day of tetracycline and 2400 mg/day of ibuprofen by themselves were not significantly different from placebo, while their combined use was significantly different. This shows the added effect of combined use together with ibuprofen, but when considering the high number of dropouts due to adverse events and that the administrated dose of ibuprofen was much larger than the usage dose in Japan, this cannot be said to be sufficient evidence for promoting oral ibuprofen.

Based on the above, we do not recommend oral NSAIDs to treat inflammatory acne lesions.

REFERENCE

98 Wong RC, Kang S, Heezen JL, Voorhees JJ, Ellis CN. Oral ibuprofen and tetracycline for the treatment of acne vulgaris. *J Am Acad Dermatol* 1984; **11**: 1076–1081. (evidence level II)

CQ16: Is chemical peeling effective for inflammatory acne lesions?

Strength of recommendation: C1 (glycolic acid [GA], salicylic acid in macrogol) or C2 (salicylic acid in ethanol).

Recommendation: We recommend chemical peeling using GA or salicylic acid in macrogol as an alternative to treat inflammatory acne lesions, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments: Because inflammatory acne lesions occur when comedones become inflamed, it is thought that inflammatory acne lesions can be reduced as a result of improving comedones with GA, lactic acid and other α-hydroxy acids (AHA), as well as salicylic acid. Their effectiveness has been reported in Japanese clinical studies, including one left–right RCT[99] and four before-and-after studies[100–103] on GA as well as one left–right RCT[104] on macrogol-base salicylic acid. Adverse events for both agents are reported to be transient irritation, dryness and scabbing. These treatments are not covered by health insurance in Japan and they have not been compared with other treatments. Based on the above, we recommend chemical peeling using GA or salicylic acid in macrogol as an alternative to treat inflammatory acne lesions if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan and sufficient informed consent is required. Moreover, actual treatment must be performed with agents of appropriate concentration and pH according to the symptoms and skin condition of the relevant patient.

Furthermore, although many European and US reports[105,106] have also shown the effectiveness of homecare treatments using low-concentration GA, salicylic acid in ethanol alone and in combination, no such reports exist in Japan and it has not been compared with peeling conducted at medical institutions.

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Glycolic acid

Strength of recommendation: C1.

Recommendation: We recommend chemical peeling using GA as an alternative to treat inflammatory acne lesions, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments: The effects of GA are greatly influenced by concentration and pH. The results of the various studies are also difficult to compare directly because of slight differences between the methods implemented by the practitioners. One Japanese left–right RCT[107] has shown that treatment using 40% GA (pH 2.0) every 2 weeks for a total of five treatments is significantly more effective than placebo, from the first treatment, for reducing both inflammatory and non-inflammatory acne lesions. GA peeling is thought to be highly effective for inflammatory acne lesions, on the basis of Japanese before-and-after studies[108–111] that have shown its effectiveness after one to four treatments. Moreover, although there is temporary irritation, there are no continuous adverse events. This treatment is not covered by health insurance in Japan and it has not been compared with other treatments.

Based on the above, we recommend chemical peeling using GA as an alternative to treat inflammatory acne lesions. Informed consent is required because the treatment is not covered by health insurance in Japan and the concentration and pH of GA should be adjusted to the skin condition of the relevant patient.

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Salicylic acid in macrogol

Strength of recommendation: C1.

Recommendation: We recommend chemical peeling using salicylic acid in macrogol as an alternative to treat inflammatory acne lesions, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments: There is one left–right RCT[112] on a special-formula salicylic acid in macrogol that has shown that treatment every 2 weeks for a total of six treatments is significantly more effective than placebo in reducing both inflammatory and non-inflammatory acne lesions after 2 months. This treatment is not covered by health insurance in Japan and it has not been compared with other treatments. Based on the above, we recommend chemical peeling using salicylic acid in macrogol as an alternative to treat inflammatory acne lesions. Informed consent is required because the treatment is not covered by health insurance in Japan.

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Salicylic acid in ethanol

Strength of recommendation: C2.

Recommendation: We currently do not recommend chemical peeling using salicylic acid in ethanol to treat inflammatory acne lesions. It must also be taken into consideration that this is not covered by health insurance in Japan.

Comments: There is one Japanese clinical study[113] where 20% salicylic acid in ethanol was used to treat 30 cases every 2 weeks for a total of five treatments, which showed after before-and-after comparison that it significantly reduced comedones, papules and pustules. This is a treatment not widely used in Japan and adverse events include erythema, irritation, dryness and scabbing, which is why we set the strength of recommendation to C2.

Based on the above, we currently do not recommend chemical peeling using salicylic acid in ethanol to treat inflammatory acne lesions. Moreover, informed consent is required because the treatment is not covered by health insurance in Japan and there is a risk of adverse events such as scabbing and erythema.

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CQ17: Is phototherapy effective for inflammatory acne lesions?

Strength of recommendation: C2.

Recommendation: Blue light phototherapy may be used to treat inflammatory acne lesions (mild to moderate) and

photodynamic therapy (PDT) to treat inflammatory acne lesions (moderate to severe). However, considering equipment and drug issues, as well as a lack of review in Japan and lack of cover by health insurance in Japan, we do not recommend it.

Comments: Blue light therapy (407–420-nm wavelength phototherapy) is effective for acne as it hits *P. acnes*-producing porphyrin with blue light, which generates singlet oxygen, one of the major ROS, that kills *P. acnes*.

One left–right study[114] comparing radiated and unradiated groups, and one left–right study report[116] comparing blue light therapy to topical CLDM 1% lotion, showed it to be effective for mild to moderate inflammatory acne lesions, with the same reducing effect as topical CLDM. There are reports[115–119] where portable phototherapy units for homecare were used to treat patients either with only blue light, with blue and red light (635–670-nm wavelength) in combination or with only red light. All these treatments showed significant reductions of acne lesions, but acquiring the same therapy units in Japan is difficult, and there is little evidence for the effectiveness of these treatments in Japan.

Based on the above, we hold that blue light phototherapy may be used to treat mild to moderate inflammatory acne lesions, although we do not recommend it.

Photodynamic therapy involves the topical application of aminolevulinic acid, which is a precursor to porphyrin, and beaming light at a wavelength within the photoabsorption band of porphyrin. The functional mechanism involves selectively exposing the aminolevulinic acid contained in the pilosebaceous system to red light, which excites porphyrin and generates singlet oxygen, one of the major ROS, that allegedly kills *P. acnes* and also destroys sebaceous glands.

There are reports from left–right studies[120–124] where phototherapy was preceded by the application of topical aminolevulinic acid on half of the face of acne patients, with either mild to moderate or moderate to severe inflammatory acne lesions. The other half of the face was either left untreated or treated with topical placebo solution. Other left–right studies[125,126] involved phototherapy, preceded by the application of methyl aminolevulinate on half of the face of acne patients with moderate to severe inflammatory acne lesions, while the other half was either treated with topical placebo solution or left untreated. These studies showed that these treatments significantly reduce inflammatory acne lesions. However, another report[127] contradicts this effectiveness on the basis of a concurrent-control study with topical adapalene, which did not show any significant treatment effect on Asian patients. Reported adverse events include pain during radiation, as well as transient but frequent post-treatment erythema, edema, irritation and burning sensation.

Based on the above, we hold that PDT may be used to treat moderate to severe inflammatory acne lesions. However, we do not recommend it as it involves the use of aminolevulinic acid, which is unapproved under the Japanese Pharmaceutical Affairs Law, is not covered by health insurance in Japan and has not been compared with other treatments.

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CQ18: Is adapalene 0.1% gel effective for comedones?

Strength of recommendation: A.

Recommendation: We strongly recommend adapalene 0.1% gel to treat comedones.

Comments: Adapalene is a drug that is highly effective for improving comedones, normalizing keratinization in the follicular epithelium and preventing the formation of new comedones. As such, it also prevents the inflammatory acne lesions that appear after comedones.

Several overseas RCT have shown that topical therapy using adapalene 0.1% gel reduces inflammatory acne lesions. According to a meta-analysis[128] that summarizes five RCT, treatment using topical adapalene 0.1% gel over 12 weeks reduced comedones by 58.1%. In the overseas studies, approximately 80% of patients suffered adverse events such as desquamation, erythema and skin dryness, and approximately 20% experienced burning sensation and itching. However, the majority of cases were mild and almost never warranted discontinued use. Moreover, Japanese RCT[129,130] have shown similar effects and adverse events for topical adapalene 0.1% as the overseas reports.

Evidence[131–134] has been gathered in Japan, showing that the combined use of adapalene 0.1% gel together with non-comedogenic moisturizer from the start does not obstruct the clinical effects of adapalene 0.1% gel, and reduces symptoms such as skin irritation, scales and erythema. This has the effect of reducing the number of treatment dropouts due to adverse events. However, there is no evidence showing the effectiveness of the moisturizer for acne, and thus it is not covered by health insurance in Japan. Moreover, there is no evidence regarding the order in which adapalene and moisturizer should be applied.

Based on the above, we strongly recommend adapalene 0.1% gel to treat comedones.

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CQ19: Is BPO 2.5% gel effective for comedones?

Strength of recommendation: A.

Recommendation: We strongly recommend BPO 2.5% gel to treat comedones.

Comments: BPO is known to have the effect of peeling the stratum corneum, from an experimental system using samples of human stratum corneum obtained with a tape-stripping method,[135] and from observing rabbit comedone models through an electron microscope.[136]

One Japanese 3-month RCT has shown that BPO 2.5% gel has a non-inflammatory eruption reduction rate of 56.5%, providing a highly significant improvement compared with the placebo at 21.9%. Adverse events included erythema and desquamation where applied, but these were within tolerable limits.[137]

Based on the above, we strongly recommend BPO 2.5% gel to treat comedones.

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CQ20: Is fixed-dose combination gel of adapalene 0.1% and BPO 2.5% effective for comedones?

Strength of recommendation: A.

Recommendation: We strongly recommend fixed-dose combination gel of adapalene 0.1% and BPO 2.5% to treat comedones.

Comments: Adapalene improves comedones through a retinoid-like effect. BPO is thought to improve comedones by directly destroying corneodesmosomes. As such, their combined use can be expected to have a complementary effect. These guidelines strongly recommend the use of both adapalene 0.1% gel and BPO 2.5% gel to treat comedones and inflammatory acne lesions.

Overseas clinical studies have shown that combination drugs of the two are more effective for comedones than each drug by itself. However, it is known that the frequency of skin irritation symptoms also increases.[138,139] One Japanese RCT involving acne patients with at least 20 facial comedones[140] has shown that the combination drug is significantly more effective after 2 weeks compared with adapalene 0.1% gel, and that this is maintained for 12 weeks. However, it was not shown that the combination drug is more effective than BPO 2.5% gel. The Japanese study also reported that the frequency of skin irritation symptoms was higher for the combination drug than the individual drugs.[140] As such, the instructions recommend considering the use of the individual drugs for treatment before the combined drug.

Based on the above, we strongly recommend fixed-dose combination gels of adapalene 0.1% and BPO 2.5% to treat comedones.

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CQ21: Is fixed-dose combination gel of CLDM1%/BPO3% effective for comedones?

Strength of recommendation: A.

Recommendation: We strongly recommend fixed-dose combination gel of CLDM to treat comedones with inflammatory acne lesions. However, we do not recommend it for maintenance therapy after the inflammatory acne lesions have subsided.

Comments: The BPO contained in CLDM1%/BPO3% fixed-dose combination gel is known to be effective for comedones.

There are two high-quality LII RCT (one overseas,[141] one Japanese)[142] on CLDM1%/BPO3%. These studied acne patients with moderate to severe inflammatory acne lesions during a treatment period of 12 weeks and covered 1315[141] and 800[142] cases, respectively. The former was a double-blind RCT comparing four groups administrated CLDM1%/BPO3%, CLDM 1% gel, BPO 3% gel and placebo. CLDM1%/BPO3% was shown to significantly reduce the number of non-inflammatory acne lesions more effectively than CLDM1% gel and placebo. Adverse reactions were mild, with two cases of contact dermatitis and photosensitive dermatitis at the site of application.

The latter was a double-blind RCT comparing three groups administrated CLDM1%/BPO3% (twice a day), CLDM1%/BPO3% (once a day) and CLDM 1% (twice a day). CLDM1%/BPO3% (twice a day) and CLDM1%/BPO3% (once a day) were shown to significantly reduce the number of total lesions including non-inflammatory acne lesions more effectively than CLDM 1% gel (twice a day).[142] Reported adverse reactions were one case each of severe facial erythema, edema and contact dermatitis, as well as 17 cases (CLDM1%/BPO3%, once a day), 27 cases (CLDM1%/BPO3%, twice a day) and seven cases (CLDM1%, twice a day) of contact dermatitis.[142]

Because there is currently no evidence on long-term maintenance therapy using CLDM1%/BPO3%, we do not recommend the long-term, continuous use of topical CLDM due to the risk of *P. acnes* acquiring resistance against antimicrobials. Based on the above, we strongly recommend CLDM1%/BPO3% to treat comedones with inflammatory acne lesions, but do not recommend it for maintenance therapy after the inflammatory acne lesions have subsided.

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CQ22: Are topical antimicrobials effective for comedones?

Strength of recommendation: C2.

Recommendation: We do not recommend topical antimicrobials to treat comedones.

Comments: Six high-quality LII RCT on topical CLDM 1% that also evaluate its effects on comedones in acne vulgaris have been reported overseas. There are three reports[143–145] showing that this drug significantly reduced both open and closed comedones, two reports[146,147] showing that it had no effect on closed comedones, and one report[148] showing that it had no effect on both comedone types. There are no Japanese references evaluating the effects of topical CLDM or ozenoxacin on comedone numbers.

Two high-quality LII RCT[149,150] on topical NDFX have been reported overseas, showing that it significantly reduces the inflammatory acne lesions of both open and closed comedones, and is more effective than topical 2% erythromycin. In Japan, one randomized, double-blind study[151] and two non-randomized studies have been reported. However, no definite results have been gained on CLDM, while there are only five reports on NDFX.

There is insufficient basic data on the effectiveness of antimicrobials on comedones and there is no evidence regarding their functional mechanisms. Such treatment is not covered by health insurance in Japan and the Global Alliance strongly advises to avoid single use of topical antimicrobials, due to the risk of *P. acnes* acquiring resistance to antimicrobials.[152]

Based on the above, we do not recommend topical antimicrobials to treat comedones.

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CQ23: Is *Kampo* effective for comedones?

Strength of recommendation: C1 (*Keigairengyoto*) or C2 (*Orengedokuto*, *Jumihaidokuto*, *Keishibukuryogan*).

Recommendation: We recommend *Keigairengyoto* as an alternative to treat comedones if other treatments are ineffective or cannot be implemented. *Orengedokuto*, *Jumihaidokuto* and *Keishibukuryogan* may be used, but we do not recommend them.

Comments: A variety of *Kampo* have been used to treat acne, such as *Orengedokuto*, *Jumihaidokuto*, *Keigairengyoto*, *Seijobofuto* and *Keishibukuryogan*.[153–160] However, the great majority of clinical evaluations have looked at the effects of *Kampo* on inflammatory acne lesions, while those examining their effects on comedones have been exceedingly scarce.[153,154,160] There is one report[153] showing that *Orengedokuto* and *Jumihaidokuto* effectively reduce or eliminate comedones, papules and pustules, when used in combination with CLDM lotion, betamethasone valerate lotion containing 1% gentamicin sulfate or topical sulfur lotion. Another report[154] showed the higher effectiveness of combination of *Keigairengyoto* together with one of the tetracyclines than of one of the tetracyclines alone. The other report[160] describes experiences of using *Keigairengyoto* together with *Inchinkoto*. We cannot evaluate decoction due to a serious lack of evidence. Even so, when considering that adverse events are minimal, the above Kampo can become an alternative if other treatments are resisted or cannot be implemented. Only acne treatment using *Keigairengyoto* and *Seijobofuto* is covered by health insurance in Japan.

Based on the above, we recommend *Keigairengyoto* as an alternative to treat comedones if other treatments are resisted or cannot be implemented. *Orengedokuto*, *Jumihaidokuto* and *Keishibukuryogan* may be administrated, but we do not recommend them.

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CQ24: Is chemical peeling effective for comedones?

Strength of recommendation: C1 (GA, salicylic acid in macrogol) or C2 (salicylic acid in ethanol).

Recommendation: We recommend chemical peeling using GA or salicylic acid in macrogol as an alternative to treat comedones, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments: GA, lactic acid and other AHA correct abnormal keratinization around the follicular epithelium and improve comedones by peeling the stratum corneum. Their effectiveness has been reported in Japanese clinical studies, including one left–right RCT[161] and four before-and-after studies[162–165] on GA, as well as one left–right RCT[165] and one left–right study[167] on macrogol-base salicylic acid. Adverse events for both agents are reported to be transient irritation, dryness and scabbing without long-term effects. These treatments are not covered by health insurance in Japan and have not been compared with other treatments.

Based on the above, we recommend chemical peeling using GA or salicylic acid in macrogol as an alternative to treat acne (comedones) if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan and sufficient informed consent is required. Moreover, actual treatment must be performed with agents of appropriate concentration and pH according to the symptoms and skin condition of the relevant patient.

Furthermore, although many European and US reports[168,169] have also shown the effectiveness of homecare treatments using low-concentration GA, salicylic acid in ethanol alone and

in combination, no such reports exist in Japan and these treatments have not been compared with peeling conducted at medical institutions.

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Glycolic acid

Strength of recommendation: C1.

Recommendation: We recommend chemical peeling using GA as an alternative to treat comedones, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments:3 GA is a agent whose effects are greatly influenced by concentration and pH. The results of the various studies are also difficult to compare directly because of slight differences between the methods implemented by the practitioners. One Japanese left–right RCT[170] has shown that treatment using 40% GA (pH 2.0) every 2 weeks on a total of five occasions is significantly more effective than placebo, from the first treatment, for reducing both inflammatory and non-inflammatory acne lesions. GA peeling is thought to be highly effective for inflammatory acne lesions, also on the basis of Japanese before-and-after studies[171–174] that have shown its effectiveness after one to four treatments. Moreover, although there is temporary irritation, there are no continuous adverse events. This treatment is not covered by health insurance in Japan and it has not been compared with other treatments.

Based on the above, we recommend chemical peeling using GA as an alternative to treat comedones. Informed consent is required because the treatment is not covered by health insurance in Japan and the concentration and pH of GA should be adjusted to the skin condition of the relevant patient.

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170 Kaminaka C, Uede M, Matsunaka H, Furukawa F, Yamomoto Y. Clinical evaluation of glycolic acid chemical peeling in patients with acne vulgaris: a randomized, double-blind, placebo-controlled, split-face comparative study. *Dermatol Surg* 2014; **40**: 314–322. (evidence level II)

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Salicylic acid in macrogol

Strength of recommendation: C1.

Recommendation: We recommend chemical peeling using salicylic acid in macrogol as an alternative to treat comedones, if standard treatments are ineffective or cannot be implemented. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments: There is one left–right RCT[175] on a special-formula salicylic acid in macrogol that has shown that treatment every 2 weeks on a total of six occasions is significantly more effective than placebo in reducing both inflammatory and non-inflammatory acne lesions after 2 months. It has also been shown to reduce comedones by 75% in a left–right study[176] over a total of five occasions. This treatment is not covered by health insurance in Japan and it has not been compared with other treatments.

Based on the above, we recommend chemical peeling using salicylic acid in macrogol as an alternative to treat comedones. Informed consent is required, because the treatment is not covered by health insurance in Japan.

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Salicylic acid in ethanol

Strength of recommendation: C2.

Recommendation: We currently do not recommend chemical peeling using salicylic acid in ethanol to treat comedones. It must also be taken into consideration that this is not covered by health insurance in Japan.

Comments: One Korean study[177] using 30% salicylic acid in ethanol on 35 cases (Fitzpatrick skin type III and IV) of patients with mild to moderate acne every 2 weeks reported that the average number of comedones had gone down from 43 to 28 after 12 weeks, while the average number of inflammatory acne lesions had gone down from 25 to 11 in the same period. Adverse events included three patients (8.8%) experiencing erythema for at least 2 days. There is also one Japanese clinical study[178] where 20% salicylic acid in ethanol was used to treat 30 patients, every 2 weeks on a total of five occasions. Before-and-after comparison showed that this treatment significantly reduced comedones, papules and pustules. This is a treatment not widely used in Japan and adverse events include erythema, irritation, dryness and scabbing, which is why we set the strength of recommendation to C2.

Based on the above, we currently do not recommend chemical peeling using salicylic acid in ethanol to treat comedones. Moreover, informed consent is required because the treatment is not covered by health insurance in Japan, and carries the risk of adverse events such as scabbing and erythema.

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CQ25: Are oral antimicrobials effective for nodulocystic lesions with inflammation?

Strength of recommendation: C1.

Recommendation: We recommend oral antimicrobials as an alternative to treat nodulocystic lesions with inflammation.

Comments: There is one report[179] on treating cystic acne with tosufloxacin that has shown effectiveness rates of 50–90%, clinically verified improvement of 57–90%, a usefulness rate of 70% and no adverse events, as well as one report[180] that has shown tosufloxacin to reduce acne lesions by 65.2%. It is thought that any treatment of inflammation will have the same effect as treatment of inflammatory acne lesions. However, the effectiveness of oral antimicrobials has not been demonstrated for nodulocystic lesions that do not present with inflammation.

Based on the above, we recommend oral antimicrobials as an alternative to treat nodulocystic lesions with inflammation. However, it is not recommended for nodulocystic lesions without inflammation.

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CQ26: Are local steroid injections effective for nodulocystic lesions with inflammation?

Strength of recommendation: B.

Recommendation: We recommend local steroid injections into cysts with inflammation.

Comments: There are reports on the effectiveness of local steroid injections for acne cysts, using betamethasone and triamcinolone,[181,182] but no related reports on nodules. Levine *et al.*[182] report that triamcinolone injections into cysts clearly improved them in a placebo-controlled RCT. Parish *et al.*[181] showed a great reduction in size in their non-randomized clinical trial. It is not clear from the results of these two studies which of betamethasone and triamcinolone is more effective. Injections outside cysts may cause skin atrophy. Oral retinoid is recommended overseas as cysts do not easily respond to antimicrobials, but it cannot be used in Japan.

Based on the above, we recommend local steroid injections inside cysts accompanying inflammation as a local-therapy alternative to oral retinoid. We do not recommend systemic administration (i.m. and s.c. injections) due to a lack of evidence regarding its effectiveness.

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CQ27: Is adapalene 0.1% gel effective for maintaining remission after inflammation has subsided?

Strength of recommendation: A.

Recommendation: We strongly recommend adapalene 0.1% gel for maintaining remission after inflammation has subsided.

Comments: Although topical retinoids and oral or topical antimicrobials may improve acne inflammatory acne lesions, they often recur after treatment has stopped. However, long-term continuous use of topical or oral antimicrobials to prevent relapse should be avoided due to the risk of resistant bacteria.

One RCT[183] involving patients with moderate to severe inflammatory acne lesions investigated the relapse-suppressing effects of adapalene. Patients with improved symptoms by first using combination therapy of adapalene 0.1% gel together with oral 100 mg doxycycline or oral 100 mg doxycycline by itself as pretreatment lasting 12 weeks were then divided into an adapalene 0.1% gel group and a gel base group, and topically applied them for 16 weeks. The maintenance therapy was deemed successful if the number of inflammatory acne lesions

that recurred during maintenance therapy was less than half of the number that disappeared during the first stage of treatment. The adapalene 0.1% gel group had a maintenance success rate of 75% in the 16th week, compared with the 54% of the gel base group. Although adverse events during maintenance therapy included itching, erythema, dryness and desquamation, there were no differences between the groups. According to a study[184] on the effects and safety of long-term use of adapalene 0.1% gel for Japanese acne patients, the majority of adverse events appeared within 2 weeks of starting treatment, with 1.8% of cases (8/446 cases) having to drop out. Furthermore, comedones and inflammatory acne lesions were significantly reduced 1 week after starting treatment. This reduction persisted throughout the 1-year trial period. As for the overseas data, the Japanese report showed that continuous use of adapalene 0.1% gel after inflammatory acne lesions have subsided has a significant effect on maintaining remission when compared with no treatment.[185] Moreover, another study compared a group applying the drug on consecutive days and a group applying it twice a week during maintenance therapy, showing that this made no difference to clinical effect or QOL.[186]

Based on the above, we strongly recommend adapalene 0.1% gel for maintaining remission after inflammation has subsided.

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CQ28: Is BPO 2.5% gel effective for maintaining remission after inflammation has subsided?

Strength of recommendation: A.

Recommendation: We strongly recommend BPO 2.5% gel for maintaining remission after inflammation has subsided.

Comments: As BPO is a strong oxidant, it easily breaks up into free radicals and is thought to improve inflammatory acne lesions by an antibacterial effect on *P. acnes*. As there have been no reports of resistant bacteria, BPO is an antibacterial drug suitable for maintenance therapy. Moreover, BPO has the effect of peeling the stratum corneum, proved by an experimental system using samples of human stratum corneum obtained with a tape-stripping method,[187] and observation of rabbit comedone models through an electron microscope.[188] These results support its efficacy for not only inflammatory acne lesions but also comedones.

A Japanese clinical study has shown the safety and effectiveness of this drug over a long treatment period of 52 weeks, with an inflammatory eruption reduction rate of 75.0% and a comedone reduction rate of 76.6% at the end of the period. Adverse events included irritation, erythema, itching, dryness and peeling where applied, but these were tolerable.[189]

Based on the above, we strongly recommend BPO 2.5% gel for maintaining remission after inflammation has subsided.

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CQ29: Is fixed-dose combination gel of adapalene 0.1% and BPO 2.5% effective for maintaining remission after inflammation has subsided?

Strength of recommendation: A.

Recommendation: We strongly recommend fixed-dose combination gel of 0.1% adapalene and 2.5% BPO for maintaining remission after inflammation has subsided.

Comments: Adapalene and BPO clinically improve comedones by different mechanisms. Moreover, while BPO is also effective against *P. acnes*, there have been no reports of resistant bacteria. Both have been used in 1-year long-term clinical studies in Japan and these guidelines also strongly recommend them for remission maintenance therapy.

In one overseas clinical study, severe acne vulgaris patients were first treated with a combination gel of adapalene 0.1% and BPO 2.5% for 12 weeks and then treated continuously with the same combination drug for another 24 weeks. It was shown that the combination drug was significantly more effective at suppressing relapse than placebo.[190]

One Japanese 1-year long-term clinical study involving acne patients with at least 20 non-inflammatory acne lesions and with 12–100 inflammatory acne lesions on the whole face,[191] showed a trend of reduced inflammatory and non-inflammatory acne lesions from the 1st week of topical treatment compared with the baseline, which persisted for the full year. The instructions recommend considering the use of the individual drugs for treatment before the combination drug due to a higher risk of skin irritation.

Based on the above, we strongly recommend fixed-dose combination gel of 0.1% adapalene and 2.5% BPO for maintaining remission after inflammation has subsided.

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CQ30: Is oral tranilast effective for hypertrophic acne scars?

Strength of recommendation: C2.

Recommendation: Oral tranilast may be used to treat hypertrophic acne scars, but we do not recommend it.

Comments: Tranilast suppresses not only the production and release of chemical mediators, such as histamine, from mast cells, but also the production and secretion of transforming growth factor-β1 from fibroblasts and inflammatory cells. It is covered by health insurance in Japan when treating keloids and hypertrophic scars. It is also used to treat hypertrophic acne scars, but there is insufficient evidence to promote it because no clinical studies have been conducted.

Based on the above, we hold that oral tranilast may be used to treat hypertrophic acne scars, although we do not recommend it.

CQ31: Are local steroid injections effective for hypertrophic acne scars?

Strength of recommendation: C1.

Recommendation: We recommend local steroid injections as an alternative to treat hypertrophic acne scars.

Comments: Local steroid injections are established as a treatment method for keloids and hypertrophic scars, and a clinical study on its effects on hypertrophic acne scars has been conducted, comparing it with cryotherapy using liquid nitrogen.[192] This study has shown that cryotherapy and local steroid injections are equally effective when judging by the size of scars. However, it should be taken into consideration that cryotherapy is not a common treatment method for keloids and hypertrophic scars, and is not covered by health insurance in Japan.

Based on the above, we recommend local steroid injections as an alternative to treat hypertrophic acne scars. Cryotherapy may be conducted, but we do not recommend it.

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CQ32: Are filler injections effective for atrophic acne scars?

Strength of recommendation: C2.

Recommendation: Filler injections (collagen, hyaluronic acid) may be used to treat atrophic acne scars, but we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan.

Comments: There are overseas case-series studies of improved sunkenness following filler injections of bovine collagen or non-animal hyaluronic acid into atrophic acne scars.[193,194] Recently, a case-series study[195] in which sunkenness was improved by filler injections of microspheres made of polymethyl methacrylate in collagen as well as an RCT[196] where its significant improvement was observed compared with control groups have been reported. However, there are only a few reports providing sufficient evidence, and no reports on Japanese patients.

Based on the above, we hold that filler injections (collagen, hyaluronic acid) may be used to treat atrophic acne scars, although we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan.

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CQ33: Is chemical peeling effective for atrophic acne scars?

Strength of recommendation: C2.

Recommendation: Chemical peeling using trichloroacetic acid or concentrated GA may be used to treat atrophic acne scars, but we do not recommend it. It must also be taken into consideration that this is not covered by health insurance in Japan.

Comments: There are reports of using 30% salicylic acid in macrogol,[197] GA[198] and 100% trichloroacetic acid[199] for treatment, but their evidence levels are low. No study has been conducted that evaluate and examine in detail degrees of acne scarring. One particular report, using 100% trichloroacetic acid, with 50.3% of patients giving positive feedback but 46.7% dropping out within three treatments, reveals the need for developing an objective method of evaluating treatment effect and for improving treatment methods. At the same time, one overseas RCT[198] compared a chemical peeling group treated with high-concentration GA (20–70%) every 2 weeks, a homecare group using a combination cream of low-concentration GA (15%) and a homecare group using placebo cream, reporting that the chemical peeling group had seen a significant effect, but seven out of the 23 patients dropped out and four were observed to suffer from long-term erythema and desquamation. We set the strength of recommendation to C2, as no conclusive evaluation of the method has been made in

Japan and the treatment carries the adverse events of swelling and stinging.

As there currently is no treatment method to promote for atrophic scars, we hold that chemical peeling using trichloroacetic acid and high-concentration GA may be used to treat atrophic acne scars, although we do not recommend it. Moreover, any actual treatment requires sufficient informed consent because the treatment is not covered by health insurance in Japan, evaluation of treatment effects is insufficient and there is the risk of adverse events.

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CQ34: Is surgical intervention effective for hypertrophic acne scars and keloids?

Strength of recommendation: C2 (surgical excision and cryotherapy).

Recommendation: Surgical excision and cryotherapy may be used to treat hypertrophic acne scars and keloids, but we do not recommend them.

Comments: Local steroid injections are established as a treatment method for keloids and hypertrophic scars, and a clinical study on their effects on acne keloids has been conducted, in comparison with cryotherapy using liquid nitrogen.[200] This study has shown that cryotherapy and local steroid injections are of similar efficacy when judging by the size of scars. However, it should be taken into consideration that cryotherapy is not a common treatment method for hypertrophic scars and keloids, and is not covered by health insurance in Japan.

Surgical excision of hypertrophic scars and keloids may be attempted when a lesion is severe and there is a functional disorder, but this treatment is administrated in combination with radiation and compression therapy, because the risk of relapse is high with simple excision. There are no reports that confirm the effectiveness of surgical excision for hypertrophic acne scars and keloids, but it may well be considered if a lesion is advanced and other treatments seem ineffective. This treatment requires sufficient informed consent regarding the risk of relapse, as well as combination therapy to prevent such relapse.

Based on the above, we hold that cryotherapy and surgical excision may be used to treat hypertrophic acne scars and keloids, although we do not recommend it.

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CQ35: Is topical azelaic acid effective for comedones and inflammatory acne lesions?

Strength of recommendation: C1.

Recommendation: We recommend topical azelaic acid as an alternative to treat comedones and inflammatory acne lesions. However, it must be taken into consideration that this is not covered by health insurance in Japan.

Comments: Azelaic acid is a saturated dicarboxylic acid found in yeast and grains such as wheat and rye. It can suppress abnormal keratinization and sebum secretion, and has antibacterial and anti-inflammatory properties.

Fifteen RCT[201–211] involving azelaic acid have been reported overseas. Studies using controls such as placebo, tetracycline, minocycline, BPO and adapalene have also shown its usefulness for comedones and inflammatory acne lesions. Adverse events include itching, erythema and irritating sensation, but these are mild. The usefulness of combination therapy with oral minocycline and oral antimicrobials has also been demonstrated.

In Japan, a low-irritant preparation containing 20% azelaic acid has been developed, and its effectiveness and safety has been confirmed in RCT.[212,213] It is recommended as the second-best option in European guidelines,[214] but Japanese reports are limited. In Japan, it is a cosmetic ingredient and has yet to be approved as a pharmaceutical drug.

Based on the above, topical azelaic acid is recommended as an alternative treatment for comedonal and inflammatory acne lesions. However, it must be taken into consideration that topical azelaic acid is not covered by health insurance in Japan.

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CQ36: Is topical vitamin C effective for inflammatory acne lesions and post-inflammatory erythema?

Strength of recommendation: C1.

Recommendation: We recommend topical ascorbyl tetrahexyldecanoate and sodium L-ascorbyl-2-phosphate as an alternative to treat inflammatory acne lesions and post-inflammatory erythema. However, it must be taken into consideration that they are not covered by health insurance in Japan.

Comments: Ascorbic acid has an antioxidative effect and can be expected to be effective for acne, particularly inflammatory acne lesions and post-inflammatory erythema. There are many variants of vitamin C derivatives, and reports exist regarding ascorbyl tetrahexyldecanoate (VC-IP) and sodium L-ascorbyl-2-phosphate. A left–right comparison study using topical VC-IP and a base has shown that VC-IP significantly reduces post-inflammatory erythema and red papules.[215] There are three RCT[216–218] on sodium L-ascorbyl-2-phosphate, all reporting its effectiveness for inflammatory acne lesions. Because there are many types of vitamin C derivatives, differences in their effect need to be examined.

Regarding the effects of topical vitamin C derivatives on post-inflammatory erythema, no follow-up studies have been conducted and further studies are required. Moreover, because post-inflammatory erythema heals spontaneously, it is possible that the effect was incidental to the reduction of inflammatory acne lesions. It is necessary to evaluate the effects in a follow-up study by comparing the reduction timeframes. It has been reported that topical sodium L-ascorbyl-2-phosphate reduces non-inflammatory acne lesions,[216,217] but follow-up studies by other teams are required. No studies have been reported on the topical application of vitamins A, B_2, B_6 and E.

Based on the above, we recommend topical ascorbyl tetrahexyldecanoate and sodium L-ascorbyl-2-phosphate as alternatives to treat inflammatory acne lesions and post-inflammatory erythema, despite the LII and LIII evidence from clinical studies. However, it must be taken into consideration that they are not covered by health insurance in Japan.

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CQ37: Is topical sulfur preparation effective for acne?

Strength of recommendation: C1.

Recommendation: We recommend topical sulfur preparation as an alternative to treat acne.

Comments: Sulfur is thought to have defatting and stratum corneum peeling effects, and its use for acne is covered by health insurance in Japan. There is not enough evidence for promotion because no clinical studies have been conducted, but we recommend topical sulfur preparation as an alternative to treat acne based on the committee's opinion.

CQ38: Are oral contraceptives and low-dose estrogen progestin combination drugs effective for acne?

Strength of recommendation: C2.

Recommendation: Oral contraceptives and low-dose estrogen progestin combination drugs may be used to treat acne, if other treatments are insufficient and the adult female patient agrees to the resulting risk of contraception, but we do not recommend them. Because they are unapproved treatments for acne that are not covered by health insurance in Japan and may cause adverse events such as thrombosis and abnormal vaginal bleeding, sufficient informed consent is required.

Comments: Many overseas RCT have been conducted on oral contraceptives and low-dose estrogen progestin combination drugs, and they provide strong evidence for their effectiveness at improving inflammatory and comedonal lesion counts, general severity and patient self-assessment.[219] However, they have not been sufficiently compared with other treatments.[219] Moreover, it has been pointed out that complications include increased risk of cerebral infarction, thromboembolism and myocardial infarction for smokers, and potential increase of cervical cancer after long-term use. At the same time, they do not increase breast cancer and are thought to reduce ovarian and uterine cancer. Patients with high blood pressure, who smoke, who are obese or who are aged 40 years or more are advised to use it with caution or not at all.[220] They are unapproved treatments in Japan and although there are relevant

case reports and review articles,[221, 222] no large-scale RCT have been conducted, so it cannot be said there is enough experience of using it.

Based on the above, we hold that oral contraceptives and low-dose estrogen progestin combination drugs may be used to treat acne if other treatments are insufficient and the adult female patient agrees to the resulting risk of contraception, although we do not recommend them. Sufficient informed consent must be given by the patient after she has acquired information on complications and lifestyle in accordance with the 2015 OC and LEP Guidelines from the Japan Society of Obstetrics and Gynecology.[223]

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CQ39: Is spironolactone effective for acne?

Strength of recommendation: C2.

Recommendation: We do not recommend oral spironolactone to treat acne characterized by either inflammatory acne lesions or comedones.

Comments: Some overseas reviews have given spironolactone treatment evidence level grade B[224] based on small-scale RCT, but a 2012 systematic review from Cochrane[225] states that there is insufficient evidence about its effectiveness for acne. It is mainly considered for administration to women as male patients sometimes develop gynecomastia. One Japanese study[226] of 139 cases showed many problems such as menstrual irregularity, all male patients dropping out and even approximately half of female patients dropping out in the end. Spironolactone not only has adverse events such as edemas, gynecomastia and menstrual irregularity, but it is not covered by health insurance in Japan and has not been compared with other treatments.

Based on the above, we do not recommend oral spironolactone to treat acne characterized by either inflammatory acne lesions or comedones.

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CQ40: Are oral vitamins effective for acne?

Strength of recommendation: C2.

Recommendation: Oral vitamins may be used to treat acne, but we do not recommend them.

Comments: Vitamins A, B_2, B_6 and E are used as complementary oral therapy when treating acne. Regarding their functional mechanisms: vitamin A is thought to suppress keratinization in the follicular epithelium, vitamin B_2 and B_6 sebum secretion, and vitamin E generation of lipid peroxide. However, no clinical studies have been conducted to establish the effectiveness of each oral vitamin on acne, so there is not sufficient evidence for promotion.

Based on the above, we hold that oral vitamins may be used for acne, although we do not recommend them.

CQ41: Is comedo extraction effective for comedones and inflammatory acne lesions?

Strength of recommendation: C1.

Recommendation: We recommend comedo extraction as an alternative to treat comedones and inflammatory acne lesions.

Comments: Comedo extraction is a physical treatment that relieves comedo or inflammatory acne lesions by evacuating sebum accumulated inside follicles for comedones and pus for inflammatory acne lesions. It is covered by health insurance in Japan. No clinical studies have shown its effectiveness, but it is the committee's opinion that its effectiveness has already been established.

Based on the above, we recommend comedo extraction as an alternative to treat comedones and inflammatory acne lesions.

CQ42: Is laser treatment effective for acne and acne scars?

Strength of recommendation: C2.

Recommendation: Laser treatment may be used to treat acne and acne scars when good results can be expected with an understanding of the features of the various laser treatment machines. However, considering equipment issues, a lack of review in Japan and a lack of cover by health insurance in Japan, we do not recommend it.

Comments: The functional mechanisms of laser treatment differ depending on equipment and wavelength, but it is thought to kill *P. acnes*, suppress sebum secretion and remodel dermal collagen.

Wavelengths of 1320, 1450 and 1064 nm are used for infrared lasers. A left–right study using a 1.320-nm neodymium:yttrium–aluminum–garnet (Nd:YAG) laser to treat only one half of the face showed the treatment to be effective for comedones but ineffective for red papules and pustules.[227] Another left–right study showed it to be significantly effective for atrophic scars.[228] Left–right studies using 1450-nm diode lasers reported significant reduction of acne acne lesions on the

back,[229] but did not find any significant difference for facial acne.[230] Before-and-after studies using 1064 nm Nd:YAG lasers reported on its effectiveness for atrophic scars.[231,232]

One report on acne treatment using a 585-nm pulsed-dye laser (PDL) showed it to significantly reduce severity score and inflammatory and other acne lesions when compared with a non-treatment group.[233] At the same time, other left–right studies using the same protocol did not find any significant difference.[234]

There are left–right studies[235–237] involving 532-nm KTP laser treatment, which showed a significant improvement for moderate severity acne.

Two RCT[237,238] studied photopneumatic therapy, where treatment combining skin suction and intense pulsed light (IPL) radiation was applied to the faces of patients with mild to moderate acne. This treatment significantly reduced comedones and inflammatory acne lesions compared with a non-treatment group and a group using lotion for oily skin. Machines for photopneumatic therapy are not widespread in Japan and few facilities use them.

When it comes to treatment using ablative and non-ablative fractional lasers on atrophic scars, there is one left–right study on each.[239,240] Texture and atrophy scores were significantly reduced 1 month after treatment completion, and this effect persisted for 6 months. There was a tendency for ablative fractional laser to induce a higher rate of improvement than non-ablative fractional laser treatment. Japanese before-and-after studies[241,242] using non-ablative fractional lasers on atrophic scars found some degree of improvement for almost all patients, 1 month after treatment completion. There is great variety in machines and treatment methods, making it difficult to compare results. Adverse events have also been reported. Long-term observation is required to confirm the sustainability of effects achieved in short-term trials.

An RCT and a left–right study using fractional radiofrequency (RF) for atrophic scars showed it to be effective but not significantly different to non-ablative fractional laser.[243] According to a review article of a number of before-and-after studies conducted overseas,[244] improvement could be observed for at least 70% of patients with mild to moderate atrophic scars after fractional RF treatment. A Japanese before-and-after study also reported moderate improvement or higher for at least half of mild atrophic scar lesions.[245]

There are many reports, including RCT (evidence level II), on laser treatment for acne and acne scars, but no comparison has been made with standard drug therapy. Although there are many machines to choose from, none have been approved for treating acne. It is difficult to make any general evaluation on the basis of the various studies because radiation source, wavelengths, pulse width, fluence and other factors all differ from model to model. Moreover, patient choice is difficult as the effect is irregular, laser by itself may not be sufficiently effective, and effectiveness is not universal. Multiple treatments are required, costs are high and effects are sometimes only temporary. This treatment has not been sufficiently reviewed in Japan and is not covered by health insurance in Japan.

Based on the above, we hold that laser treatment may be used to treat acne and acne scars, when good results can be expected with an understanding of the features of the various laser treatment machines. However, considering equipment issues, a lack of review in Japan and a lack of cover by health insurance in Japan, we do not recommend it.

Japanese before-and-after studies[241,242,245] on fractional lasers and fractional RF have been conducted. Such treatments may be attempted when treating refractory atrophic scars, but we do not recommend them. We hope more evidence can be gathered in Japan in the future.

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CQ43: Is washing one's face effective for acne?

Strength of recommendation: C1.

Recommendation: We recommend that acne patients wash their face twice a day as an alternative.

Comments: It is difficult to conduct a comparative study on the effectiveness of washing one's face. Even the systematic review by Magin *et al.*[246] did not find sufficient evidence from clinical studies, stating that a clear conclusion cannot be reached at present. Choi *et al.*[247] reported that although there was no statistically significant difference between frequencies of washing one's face, some cases worsened by reducing the frequency from twice to once a day and there were dropouts from the group washing their face four times a day. It is reasonable to hypothesize that the removal of sebum has an acne-preventive effect, so we recommend washing one's face twice a day as an alternative.

One Japanese report has shown that acne is improved by oil cleansing and that it does not worsen the condition.[248] Therefore, there is no reason to believe that oil cleansing may worsen acne. Rather, it is a candidate for safe makeup removal. There is one report[249] showing no significant difference between detergents with or without particles for peeling the stratum corneum (scrub), so the effectiveness of scrubbing is not established. There are reports showing the effectiveness of detergents containing antibacterial substances, such as disinfectants,[250] and low-irritant detergents,[251,252] but sensitization and irritation have not been examined sufficiently. For future reference, the issue of irritation needs to be sufficiently examined when considering the detailed usefulness of ingredients contained in various products.

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CQ44: Is the use of skincare products for acne effective for acne patient?

Strength of recommendation: C1.

Recommendation: We recommend acne patients to use skincare products for acne as an alternative. However, they should carefully choose low-irritant and non-comedogenic products based on clinical trials in acne patients.

Comments: There are many reports about the usefulness of skincare products for acne. In Japan, some studies have confirmed their usefulness in combined use[253–257] or individually[258–260] of the products for acne. The products used had all been tested as low-irritant and non-comedogenic, and with moisturizing effect. If skincare products are chosen with these properties, and used with topical drugs, skincare products can be expected to lessen skin irritation from the drugs, improve treatment effect and assist to accomplish treatment.

Based on the above, we recommend acne patients to use skincare products for acne as an alternative. However, they should be careful to choose low-irritant and non-comedogenic skincare products based on clinical trials in acne patients.

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CQ45: Is makeup advice effective for acne?

Strength of recommendation: C1.

Recommendation: We recommend providing makeup advice to female acne patients for the purpose of improving QOL as an alternative. However, they should be careful to choose makeup products that are low-irritant and non-comedogenic.

Comments: It is a fact that acne may be worsened by some oily cosmetics, so makeup products that induce comedones should be avoided. However, there is no clear evidence that supports the opinion of banning all makeup because large-scale studies on makeup for acne patients have not been conducted. At the same time, there is evidence suggesting that makeup does not obstruct treatment[261–265] and improves QOL.[261–265] Therefore, there is no particular reason to restrict the use of non-comedogenic cosmetics. The use of cosmetics may still be up for debate depending on the case, but the use of low-irritant and non-comedogenic makeup products[272] is permissible.

Based on the above, we recommend providing makeup advice to female acne patients for the purpose of improving QOL as an alternative. However, they should carefully choose cosmetics that are low-irritant and non-comedogenic.

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CQ46: Is it effective to generally limit certain foods for acne patients?

Strength of recommendation: C2.

Recommendation: We do not recommend generally limiting certain foods for acne patients. When it comes to dietary advice to individual patients, we must sufficiently examine the relationship between the consumption of certain foods and acne development.

Comments: One systematic review reached the conclusion that there is no clear correlation between particular foods and acne.[266] Among the few RCT that have investigated the connection between acne and food, one denies that chocolate is an aggravating factor for acne.[267] On the other hand, it has been reported that 100% cacao powder induced acne lesions in a small-scale double-blind study,[268] inviting further trials. Besides, it has been shown that acne patients do not consume sugar in particularly large quantities and also that sugar is not related to the acne lesions.[269] One cohort study[270] analyzed the dietary intake and acne of high school students to identify milk as a critical cause of acne, but this report was contentious and called for follow-up studies with different methods. At present, there is no clear evidence to identify particular food as an aggravating factor for acne.

Based on the above, we do not recommend generally limiting certain foods for acne patients. We recommend against deviated food habits and maintaining a well-balanced diet. Moreover, when it comes to dietary advice to individual patients, we should sufficiently examine the relationship between the intake of certain foods and acne development.

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CQ47: Is dietary advice effective for acne patients?

Strength of recommendation: C2.

Recommendation: We currently do not recommend specific dietary advice for acne patients.

Comments: Two RCT reports have shown that advising acne patients to maintain a diet with low glycemic index (GI) led to an improvement of acne.[271,272] There is also a report showing that acne improved in both low-GI and high-GI diet groups without significant difference between the two groups.[273] A result of meta-analysis with the former two trials was evaluated as a low level of evidence.[274] Thus, there is not yet a unified view. GI express the relative speed by which the carbohydrates in ingested food are digested and

changed to glucose. It is used for giving dietary advice to patients such as diabetics. From prospective studies of probiotics, supplements containing lactobacilli with systemic minocycline treatment showed synergistic effects for inflammatory acne.[275] The other report showed improvement in acne with milk containing lactoferrin.[276] Regarding the effect of eicosapentaenoic acid on inflammatory acne, there are reports showing both improvement[277] and no significant improvement in acne severity.[278] Further examination of the effects of dietary advice is needed.

Based on the above, we do not recommend any specific dietary advice for acne patients at this time.

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CQ1: Are topical drugs effective for rosacea?

Strength of recommendation: C2.

Recommendation: Topical metronidazole and azelaic acid may be used to treat papulopustular rosacea, but we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan, and care should be taken to consider base and concentration.

Comments: There are no placebo-controlled data on the effectiveness of topical drugs available in Japan for erythematotelangiectatic and phymatous rosacea. Examinations have been made on the use of metronidazole and azelaic acid in topical therapy for papulopustular rosacea.

The functional mechanism of metronidazole against the pathology of rosacea is unknown, but a systematic review of 12 RCT conducted overseas has shown that it is effective for reducing the inflammatory acne lesions of papulopustular rosacea.[279] Comparisons have been made between 1% and 0.75% topical metronidazole concentrations and between cream and gel bases, but no significant differences were shown.[279] Topical metronidazole is also effective for remission maintenance after papulopustular rosacea.[280] Two Japanese clinical studies involving in-house prescription drugs have been conducted, showing effective results for 74% of patients when using 1% metronidazole ointment with a base of hydrophilic petrolatum,[281] and for 58.8% of patients when using 0.8% metronidazole ointment with a base of macrogol ointment.[282] However, metronidazole 0.7% gel is not applicable to rosacea in Japan, neither are there any reports of it being used.

Topical azelaic acid has only been examined in overseas RCT, but it is reported to have similar effectiveness as topical metronidazole, and that it increased patient compliance because its effectiveness is similar whether applied once or twice a day.[283] There is a Japanese report involving topical drugs containing azelaic acid as maintenance therapy for papulopustular rosacea patients after symptoms had subsided, following combined use with oral antimicrobials, which found both to be effective for maintenance therapy.[284] Another RCT used a combination drug of 10% sulfacetamide and 5% sulfur for topical treatment and found it to be equally effective to metronidazole, or to be significantly more effective. However, information regarding rosacea type and patient backgrounds is missing for both drugs.[285] Regarding topical antimicrobials: the effectiveness of macrolides (erythromycin, CLDM) for inflammatory acne lesions has been reported,[286,287] but we do not recommend them because treatment easily becomes long-term, increasing the risk of resistant bacteria. Moreover, no clinical studies have been reported on topical treatment of Japanese rosacea patients using azelaic acid, sulfur preparation or antimicrobials.

Based on the above reports and availability in Japan, we hold that topical metronidazole and azelaic acid may be used to treat papulopustular rosacea, but we do not recommend them.

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CQ2: Are oral drugs effective for rosacea?

Strength of recommendation: C2.

Recommendation: Oral doxycycline, minocycline and tetracycline may be used to treat papulopustular rosacea, but we do not recommend them. We currently do not recommend *Kampo* or oral ivermectin and metronidazole in cases of demodicosis.

Comments: It has been shown that the enzymes kallikrein and serine protease are highly active in rosacea lesions.[288] It is hypothesized that tetracyclines use their enzyme-inhibiting property against matrix metalloproteinase, to indirectly suppress the activity of kallikrein and serine protease in epidermal keratinocytes, thus improving the pathology of rosacea.[289] However, no clinical studies have been conducted in Japan for oral antimicrobial treatment of rosacea. Two overseas placebo-controlled RCT, using doxycycline 40 mg sustained-release tablets to treat papulopustular rosacea, showed that this treatment significantly reduced inflammatory acne lesions.[290] It has also been reported that there is no significant difference between doxycycline 40 mg sustained-release tablets and doxycycline 100 mg, when used in conjunction with topical metronidazole.[291] Moreover, doxycycline 40 mg sustained-release tablets do not have any antibacterial properties and are as yet unapproved in Japan, in contrast to the antibacterial doxycycline 50 mg tablets. A Japanese case-series study[292] treated 119 rosacea patients (type unspecified) with combined oral minocycline 100 mg (daily doses) and topical 1% metronidazole ointment, reporting high satisfaction with regards to erythema and papule symptoms. Two overseas placebo-controlled clinical studies[293,294] on tetracycline both showed the usefulness of tetracycline. Note that tetracyclines should not be administrated to pregnant patients regardless of dose, and that caution is required when treating infants due to possible adverse events, including yellowing teeth. Consideration should also be given to the risk of resistant bacteria in the case of long-term use of antimicrobials.

For *Kampo*, we only have case reports[295–297] of erythematotelangiectatic rosacea treatment using *Shishihakuhito*, *Orengedokuto*, *Kakkonkokato*, *Keishibukuryogan* and *Unseiin*, and reports of papulopustular rosacea treatment using *Keigairengyoto*, *Jumihaidokuto* and *Byakkokaninjinto*. Therefore, we cannot recommend them at present. Oral ivermectin and metronidazole can be considered for treating the demodicosis that frequently accompanies papulopustular rosacea, but we do not recommend them as there have been no reports of use in Japan and overseas evidence also is insufficient.[298] When administrating oral metronidazole, caution must be taken related to alcohol restrictions and spasms.

Based on the above, we hold that oral tetracyclines (doxycycline, minocycline, tetracycline) may be used to treat papulopustular rosacea, but we do not recommend them. There is no sufficiently reliable evidence on the effectiveness of oral therapies to treat erythematotelangiectatic and phymatous rosacea. We currently do not recommend *Kampo* or oral ivermectin and metronidazole in the case of demodicosis due to insufficient evidence.

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CQ3: Are laser treatment and phototherapy effective for rosacea?

Strength of recommendation: C2.

Recommendation: PDL (595 nm), Nd:YAG laser (1.064 nm) and IPL may be used to treat erythematotelangiectatic rosacea, but we do not recommend them. It must also be taken into consideration that they are not covered by health insurance in Japan, and sufficient informed consent is required regarding the risk of relapse.

Comments: Laser and light therapy improves the symptoms of erythematotelangiectatic rosacea by reducing and shrinking capillary dilatation. PDL (595 nm) and Nd:YAG laser (1064 nm) are effective individually, but combined use has been reported to eliminate capillary dilatation more effectively.[299] Moreover, a comparison of PDL (595 nm) group and Nd:YAG lasers (1064 nm) showed that PDL (595 nm) does not cause purpura

and reduces redness more effectively, while Nd:YAG alleviated pain more effectively.[300] A systematic review reported that PDL (585, 595 nm) is also effective for papulopustular rosacea, but more data needs to be gathered.[301] A systematic review on IPL reported that it significantly reduced capillary dilatation and erythema, as for PDL.[302] Moreover, a Japanese clinical study graphically analyzed the effect of IPL for capillary dilatation, showing a significant correlation with the degree of improvement visible to the eye.[303] There are case reports of Nd:YAG[304] and CO_2 lasers[305] for surgical treatment of phymatous rosacea.

There are numerous reports on laser treatments, but treatment protocols are not uniform. It is difficult to make any general evaluation on the basis of the various studies, because radiation source, wavelengths, pulse width, energy concentration, hot spot and spot size all differ from model to model. They also have not been compared with other treatment methods. Furthermore, there are no reports on long-term efficacy and safety. Review in Japan is insufficient and the use of PDL to treat rosacea symptoms other than capillary dilatation is not covered by health insurance in Japan. More study is required.

Based on the above, we hold that PDL (595 nm), Nd:YAG laser (1.,064 nm) and IPL may be used to treat erythematotelangiectatic rosacea, although we do not recommend them. The need for actual treatment must also be determined on the basis of each patient's symptoms and skin condition. Sufficient informed consent is required because the treatment is not covered by health insurance in Japan, the effect differs between individuals and there is a risk of relapse.

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CQ4: Is skincare effective for rosacea?

Strength of recommendation: C1.

Recommendation: We recommend advice on appropriate UV light protection as well as the use of low-irritant facial cleansers and moisturizers as an alternative to treat rosacea.

Comments: Skincare for the treatment of rosacea contributes to symptom improvement by providing protection from factors that exacerbate the condition, such as UV light, temperature changes and dryness. No clinical studies have been conducted on the effectiveness of UV light protection and maintaining moisture, but it is recommended in Japan and abroad that patients opt for appropriate UV light protection as well as the use of low-irritant facial cleaners and moisturizers.[306,307] Although there is insufficient evidence, it is the committee's opinion that an adequate consensus exists, and thus we recommend it as an alternative. Moreover, camouflage makeup can also become an alternative as it can improve patient QOL. Everyday advice to the patient is also important, because the symptoms of paroxysmal erythema can be alleviated by understanding what factors stimulate it (sunlight exposure and temperature changes, among others)[308] and avoiding them.[307]

Based on the above, we recommend advice on appropriate UV light protection as well as the use of low-irritant facial cleansers and moisturizers as an alternative to treat rosacea.

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