INTRODUCTION

Acne vulgaris is an extremely common condition that affects more than 40 to 50 million individuals annually in the United States alone.[1] Although more prevalent in teenagers, acne can also have an impact in every age group.[2] Both sexes and all races are prone to this often distressing skin condition.[3] Many physicians trivialize this condition, but a considerable amount of research had been done to study the psychosocial impact and quality of life for patients suffering from acne. In fact, a study by Mallon et al. assessed the quality of life for acne patients and compared it with other chronic conditions.[4] They found that acne patients have social, psychologic, and emotional problems to the same magnitude as those with chronic asthma, epilepsy, diabetes, back pain, or arthritis. Thus, acne contributes to low self-esteem and self-confidence and often leads to anger, frustration, and social withdrawal.[5]

The key factor in the pathogenesis of inflammatory acne is the proliferation of *Proprionibacterium acnes* (*P. acnes.*) [6-8] During adolescence, hormonal changes cause increased activity of the sebaceous glands.[9, 10] This results in excess sebum production and abnormal keratinization in the sebaceous gland duct leading to the follicle.[11, 12] Obstruction of the follicle then occurs, providing a favorable environment for *P. acnes* proliferation.[13,7] Additionally, excess sebum serves as an excellent nutritional source for *P. acnes* populations.[14] This process leads to inflammation and the resultant papules and pustules observed in patients with inflammatory acne.[13]

Many treatment options for acne currently exist and a significant amount of money is spent on prescription and non-prescription medications by Americans each year.[15, 16] However, all of these treatment options have limitations. Topical acne preparations (i.e., benzoyl peroxide, retinoids) are often too irritating for patients and lead to decreased compliance.[17, 18] The mainstay of mild to moderate acne is topical and/or oral antibiotics, but in recent years resistance has become a major concern.[19-22] In addition, many patients fail with oral antibiotic therapy and need a new therapeutic modality for their acne. Topical retinoids are implemented for their effect on keratinization and anti-inflammatory properties.[19-21] These agents commonly cause a great deal of irritation for patients (i.e., peeling, dryness, erythema, stinging, burning, and photosensitivity) which preclude their use for many patients.[23-25] Isotretinoin (Roche, Nutley, New Jersey) is an effective treatment modality for acne; however, it has numerous side-effects and is reserved only for severe or refractory cases.[26, 27] Chemical peels, laser ablation, and surgery are not generally directed against active disease, but rather to improve the resultant effects of acne (scars, hyperpigmentation, etc.)[28, 29] Therefore, the need for an effective, safe, and easy-to-use modality that is not irritating for patients is highly desirable and needed.

The CHARME system is a novel hand-held medical device that electrolyzes a water-based sodium chloride solution, which effectively delivers electrolyzed oxidized water (EOW) to the skin (Figure 1). The delivery system is unique in that it produces fine particles 40 microns or less that is able to penetrate into the epidermis and upper dermis. EOW has been used for many years in Japan for its anti-microbial properties in the treatment of thermal injury, pressure ulcers, and nosocomial infections.[30-33] In addition,

EOW has been used for cleaning and disinfecting of medical equipment, such has hemodialysis units.[34-36] Studies show that the CHARME device is active against a wide range of bacteria, including anaerobes, gram-positive, and gram-negative species, and even viruses (including HIV and Hepatitis) (Table 1).[34, 37] Furthermore, the CHARME device acts through a natural occurring substance, thereby eliminating the need for artificial substances.

The effectiveness of the CHARME device in producing electrolyzed, low pH solution that is active against a wide variety of bacteria and its unique delivery system to the skin provides the basis for investigating this medical device as a potential treatment modality in mild-to- moderate acne. The purpose of this open-label pilot study was to determine the efficacy and the tolerability of the CHARME device in the treatment of mild-to-moderate acne.

METHODS

A total of 31 subjects qualified and were enrolled in this split-face, open-label clinical study. To be included, patients had to present with 5-50 facial non-inflammatory lesions (open and closed comedones), 5-60 inflammatory lesions (papules and pustules) and no more than 3 cystic lesions on each side of the face. No other dermatologic disease could be present on the face. Patients were excluded from the study if they used topical acne medications in the preceding 14 days, systemic antibiotics in the past 30 days, or systemic retinoids in the last 6 months prior to initiation of treatment. Pregnant and lactating women, as well as, women using oral contraceptives were excluded from the study. In addition, patients were not allowed use any other over-the counter acne medications or washes during the study period. Only mild moisturizers and sunscreens were permitted throughout the study. Informed consent was obtained from all participants. Minors had their informed consent co-signed by a parent or legal guardian and accompanied the subject at each visit.

At baseline, medical history and physical examination was performed. A thorough assessment of the severity of acne was evaluated and the numbers and types of acne lesions were noted. Patients were given detailed information on how to use the study device. This included demonstrations on how to pour the Base solution (low concentration of 2500 ppm NaCl solution) into the CHARME device. Demonstrations were also given by the evaluator on the distance (approximately 10 cm from the face) and duration (a minimum of 10 seconds to a maximum of 30 seconds) when using the study product. Patients were given one CHARME device, three bottles of Base solution, and two unscented Dove soap bars. At each visit, empty Base solution bottles were retrieved and recorded.

Each patient was instructed to use only unscented Dove soap to cleanse the entire face twice a day. After the face was washed and dried, the CHARME device was to be used on the right side of the face only for 10-30 seconds continuously twice daily (morning and night), while the left side of the face was untreated (control). A log sheet was

provided to each patient which kept track of the time, date, duration, and any adverse effects experienced with usage.

Efficacy and cutaneous tolerance were assessed four times over the trial period: baseline, weeks 2, 4, and 8. At each of these visits, the number and type of acne lesions were evaluated, and patient and physician assessments were recorded. Vital signs and adverse effects were also recorded at each visit and product compliance was reviewed. Telephone calls were made to each patient at 2 week intervals to stress product compliance and assess patient's general well-being. Cutaneous tolerance was assessed by determining erythema, peeling, stinging/burning, and pruritus. All cutaneous tolerance evaluations were graded on a 0-3 scale: 0-none; 1-mild; 2-moderate; 3-severe. Global improvement compared with baseline was graded by the physician at each follow-up visit using the following 6-point scale: 0-no signs of acne; 1-markedly (75%) improved; 2-moderately (50%) improved; 3-slightly (25%) improved; 4- no improvement; 5-worse. Using the same scale, patients graded improvement in their acne over the course of the treatment period. At the conclusion of the study, patient satisfaction with the CHARME device was measured using a 0-3 scale; 0-Unsatisified; 1-Fair; 2-Good; 3-Excellent. This questionnaire also included participants' assessment of the CHARME device in comparison to conventional treatments for acne based on a numerical scale.

Patients were photographed in a standardized method using high-resolution digital photography (Nikkon 990) at baseline and each visit thereafter.

Results of treatment vs. baseline scores were assessed using a Hotellings t-test and repeated measures analysis of variance. All statistical tests were 2-sided, and the values of 0.04 or less were considered statistically significant.

RESULTS

Patients

Twenty-five of the 31 participants completed the 8-week efficacy and tolerability study. Of these 31 participants, 2 subjects were disqualified for treating the entire face with the CHARME device and 4 were lost to follow-up or moved to another geographical region. The mean age was 24.7 years, with a range from 15 to 47 years. The ethnicity groups represented in this study were: White (32%), Asian (32%), Latino (20%), and African-American (16%).

Clinical Assessment

There were no significant differences between the right and left side of the face in any of the parameters to be evaluated at baseline. The mean change (reduction) in the total number of acne lesions from baseline to the end of treatment (8 weeks) was 40.9% for the right side (CHARME treated side) and 18.0% for the left side (P=.04). There was a consistent reduction in total lesion count in the CHARME treated side, with clinically

relevant reductions at Week 8, compared with an inconsistent clinical response in the untreated side (Figures 2 and 3).

The mean reduction in the number of inflammatory lesions (pustules and papules) from baseline to the end of treatment was 49.1% in the CHARME treated side compared with 9.9% in the untreated side ($P<.01$). The mean reduction in each specific type of inflammatory lesion was also clinically significant. The treated side had a mean reduction of 75.7% and 42.0% in the number of pustules and papules, respectively. The untreated side showed only a mean reduction of 19.4% and 7.38% in the number of pustules and papules, respectively ($P = 0.002$) (Figures 4 and 5).

There was not a statistically significant reduction in the number of non-inflammatory acne lesions (open/closed comedones) or cysts between the right and left side of the face ($P = 0.336$).

Physician-assessed global improvement increased steadily, as noted by in the percentage of patients improving from baseline, with 100% of patients improving by week 8 (25% or more improvement) (Figure 6). Patient-assessed global improvement in acne also steadily increased during the course of the study period. At week 8, 50% of patients graded overall improvement as moderate (50% or more improvement) for the right side of the face (Figure 7). In addition, 75% of the participants indicated that they preferred CHARME's delivery system over conventional topical acne medications.

Safety Assessment

The CHARME system was well tolerated by an overwhelming majority of the subjects. None of the participants stopped or temporarily ceased treatment due to any side effects. One subject had transient pruritis and two others had mild erythema during the first two days of treatment. Two additional subjects experienced burning/stinging and treatment associated peeling. All cutaneous side-effects resolved by Week 2 visit (Figure 8).

Patient Satisfaction Assessment

Eighty percent of the participants rated their satisfaction with the device as good or excellent, while 16% rated the CHARME as fair. Only 4% of the subjects were unsatisfied with the CHARME (Figure 9).

DISCUSSION

Electrolyzed oxidized water (EOW) is produced with an anode current by electrolyzing salt-containing water through a diaphragm.[38] EOW, which has a high positive oxidation-reduction potential (ORP) and high concentrations of dissolved chloride and oxygen, functions as a bactericide and is used clinically for the treatment of various types of infection and for cleaning and disinfecting of medical equipment.[38-40] Since the 1990s, electrolyzed NaCl solutions containing high free-chloride concentrations have been investigated for various clinical applications in Japan. Currently, two types of

electrolyzed solutions are available: electrolyzed weak acid water (EWW) and electrolyzed strong acid water (ESW). The CHARME device generates ESW by electrolysis of a NaCl solution using positive and negative electrodes in compartments separated by a cationic membrane, and is obtained from the well of the positive electrode (Figure 10).[38] This process can be summarized in the following chemical formula.[38-40]

Positive electrode:

$H_20 \rightarrow 1/2O_2 + 2H^+ + 2e^-$

$2Cl^- \rightarrow Cl_2 + 2e^-$

$Cl_2 + H_20 \leftrightarrow H^+ + Cl^- + HClO$

Negative electrode:

$2H_20 + 2e^- \rightarrow H_2 + 2OH^-$

The water at the positive electrode becomes EOW, which has a low pH and a high ORP and contains high concentrations of dissolved chloride, oxygen, and hydroxy radical. Water at the negative electrode becomes a basic aqueous solution that has a high pH and a low ORP and high concentrations of alkaline minerals.

All microorganisms require a certain mitochondrial environment for survival; a pH in the range of 2 to 12 and from -400 to 850 mV in ORP is needed in order to survive and proliferate.[41] The CHARME device produces a solution that has a pH in the range of 2.3 to 3.0 and a high ORP in the range of +1100 mV to +1300 mV.[38] It also generates high concentrations of hypochlorous acid (HClO), dissolved oxygen (9-15 ppm), and hydroxyl radicals.[38] This is the solution that is emitted in a fine mist by the CHARME device after the electrolysis process.

The EOW produced by the CHARME device clearly falls outside the required parameters for mitochondrial function of microorganisms. This serves as the basis for the proposed mechanism of action against *P. acnes* population. Additionally, the high concentrations of hypochlorous acid and hydroxy radicals produced by the CHARME solution are well-documented and potent germicidal agents that markedly increase in low pH solution. Moreover, a study by Shimizu et al. reported that almost all organisms will perish within 10 seconds in EOW due to the synergistic activity of the resultant radicals (Cl^-, hydroxyl radical, H_2O_2, etc.) generated in EOW.[42, 43] These radicals react with oxygen and destroy *P. acnes* by damaging its cell lipid membrane, denaturing proteins, and prevent replication by severing its DNA.[44] It is important to note that EOW does not provide long-lasting anti-bacterial effect after application and, therefore, repeated applications are necessary.[38, 45, 46] In this study, participants were instructed to use the CHARME device twice daily for at least 10 seconds.

To further analyze EOW's bactericidal effect, research studies on inhibiting *P. aeruginosa* growth by EOW can be used as a model. Using electron microscopy, *P. aeruginosa* growth was completely inhibited by EOW. Morphological changes noted on electron microscopy showed that EOW induced breaks and blebs in the outer membrane cell wall (average diameter of bleb was 28 nm) which were not seen in unelectrolyzed NaCl solution.[37] To assess whether the effect of EOW penetrated deep into the bacterial cells, the presence of chromosomal DNA was detected by RFLP assay.[37] No bands were detected using EOW, while bacterial samples treated with unelectrolyzed NaCl revealed strong band formation.[37]

The present study shows that the CHARME device administered twice daily for 8 weeks in patients with mild to moderate acne resulted in a 40.9% overall reduction in mean acne lesion counts. A similar reduction was noted in the mean inflammatory acne lesion counts measured independently (49.1%). An even more dramatic decrease was observed when measuring individual inflammatory lesions—75.7% for pustules and 42.0% for papules.

The mechanism by which the CHARME system improves inflammatory acne lesions is most likely due to the EOW. The EOW is anti-microbial and decreases *P. acnes* colony populations. This proposed mechanism of action is supported by our observation in that pustules followed by papules had the most significant reductions.

This study clearly demonstrates that the CHARME system is potentially effective on inflammatory lesions, but not an effective comedolytic agent; however, we suggest that by including a strong comedolytic agent, such as a topical retinoid along with CHARME in patients with inflammatory acne, the need for oral and topical antibiotics can be eliminated. Moreover, the CHARME device can work in conjunction with topical retinoids and perhaps even decrease treatment-associated cutaneous side-effects commonly experienced by patients on topical retinoids.

Patient satisfaction with CHARME rated very high—80% of the participants rated their satisfaction with the CHARME device as excellent or good. Only 4% of the subjects were unsatisfied with the CHARME. Moreover, 50% of the subjects reported a moderate improvement in their acne at week 8. Of particular importance, 75% of the subjects indicated that they would rather use a delivery system like the CHARME device rather than conventional forms of treatment.

In contrast to the likelihood of other anti-acne products (i.e., topical retinoids, benzoyl peroxide, etc.) to cause side-effects, the CHARME device and its delivery system did not produce significant clinical signs or subjective symptoms of irritation, stinging/burning, erythema, pruritis, or peeling. In fact, 96% of the patients did not experience any burning/stinging or peeling. Only 4% of the patients experienced pruritis and 8% experienced treatment associated erythema. All of the side-effects experienced by subjects during the treatment period were completely resolved by Week 2 visit.

From a pharmacoeconomic perspective, the CHARME system appears to be a cost-effective acne therapy. It is difficult to conduct a cost-effectiveness analysis on current acne therapies in comparison to the CHARME device due to the multitude of factors that go into assessing costs for acne treatment. However, when evaluating the estimated costs of various acne therapies in 2001, the CHARME device affords the patient with a more cost-effective method in treating acne.[16, 47] For instance, 40% of patients in 2001 spent an average of $293.03 on acne treatments and 20% of patients consumed an average of $813.24 per year in acne medications.[16, 47] Tolerability of these medications can also influence the overall cost since more office visits are required and alternative medications may be prescribed to increase compliance. Thus, CHARME provides a cost benefit to the patient and physician under capitation restraints from insurance companies.

Clinical studies have repeatedly shown that combination therapy yields the best results when treating acne.[19-21, 48] A common approach is to use topical or systemic antibiotics with topical retinoids.[19-21] However, topical and oral antibiotics are often associated with the emergence of resistant bacteria and adverse effects such as gram-negative folliculitis, vaginal candidiasis, discoloration of teeth, headaches, depression, gastrointestinal upset, and dose-related phototoxic effects.[49-56] Other antibiotic options, such as trimethoprim sulfamethoxazole, clindamycin, and ciprofloxacin are effective, but are limited by toxicities.[57] The present study suggests CHARME is most effective in combating inflammatory acne and, therefore, a possible alternative would be to replace oral/topical antibiotics in the management of this condition. Oral and topical antibiotics could be used as a second-line option which would undoubtedly reduce *P. acnes* resistance and antibiotic-associated toxicities.

CONCLUSION

The CHARME device and its unique delivery system to the skin appears to be a revolutionary modality in treating acne. Although it has never been studied specifically for acne, scientific evidence from other applications makes this medical device a practical and logical consideration. Used for many years in Japan, EOW has been shown to be effective against many different types of bacteria, viruses, and fungi. This study showed that the CHARME device can dramatically improve inflammatory acne lesions, namely papules and pustules.

This study also confirmed patient satisfaction and acceptance with the CHARME system. The unique delivery system is well liked by patients due to ease of use and relatively low treatment associated side-effects that are commonly experienced by topical acne regimens. In addition, the cost savings noted in using CHARME makes this device an even more attractive option for patients. Other advantages of CHARME include: relatively short duration of therapy (8 weeks), good patient compliance, and lack of antibiotic resistance. Although this is the first study illustrating the efficacy and tolerability of the CHARME device in treating acne, the results and patient satisfaction noted seem promising. Future studies will be required to see if EOW has additional mechanisms of action in treating inflammatory acne.

Figure 1. CHARME unit with charger. CHARME is a light-weight (360 grams), hand-held unit constructed with ABS plastic. The unit has a width of 64mm, depth of 74mm, and a height of 184mm.

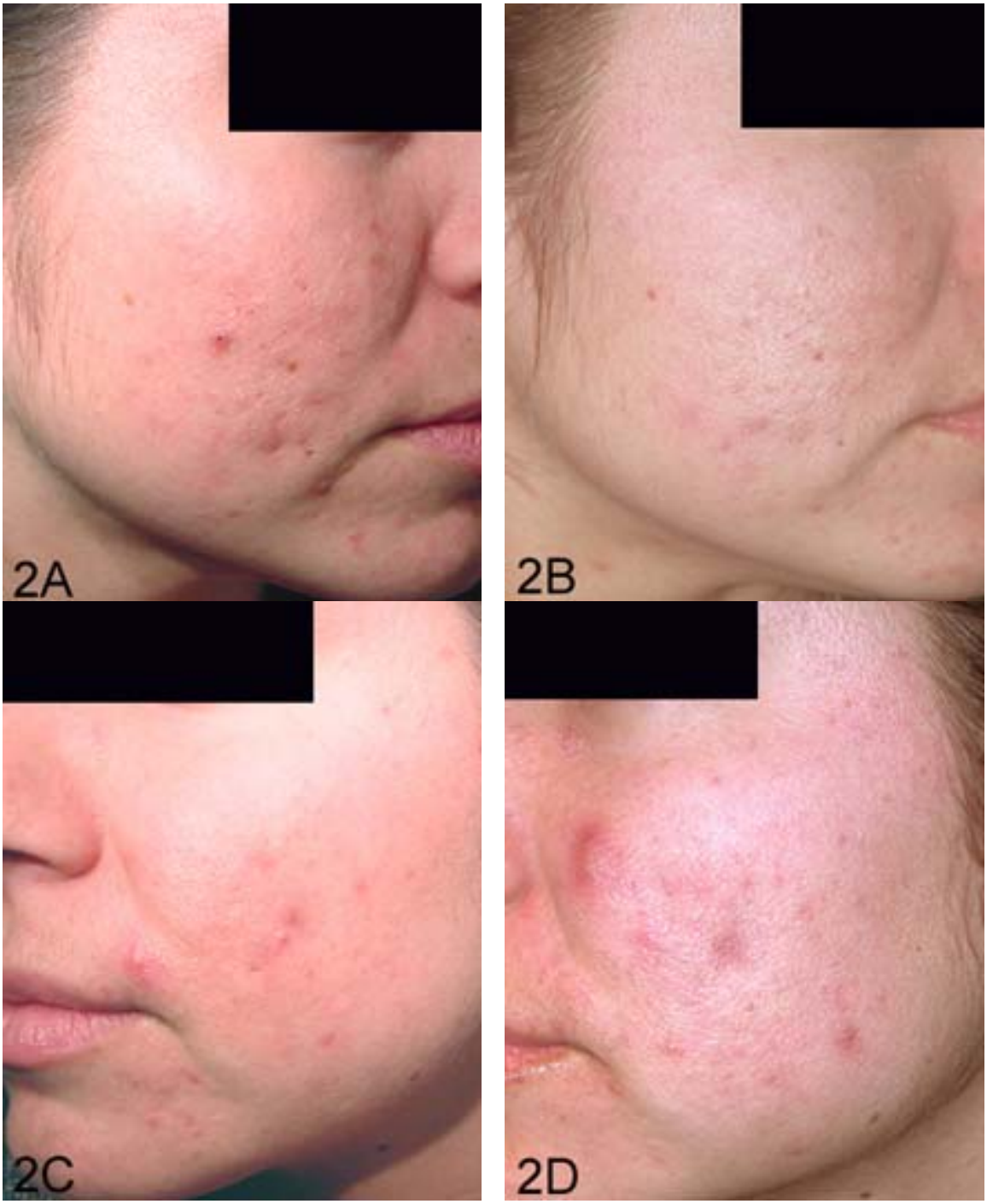

Figure 2. Patient is a 28-year old Caucasian female with long-standing inflammatory acne refractory to oral and topical antibiotics, topical retinoids and benzoyl peroxide. **2A.** Before treatment, numerous inflammatory acne lesions are noted. **2B.** After 8 weeks of treatment with CHARME twice daily, significant improvement is noted with minimal irritation. **2C.** Same patient at baseline without treatment on left side of face (control). **2D.** Control at 8 weeks. No improvement observed in acne lesion counts.

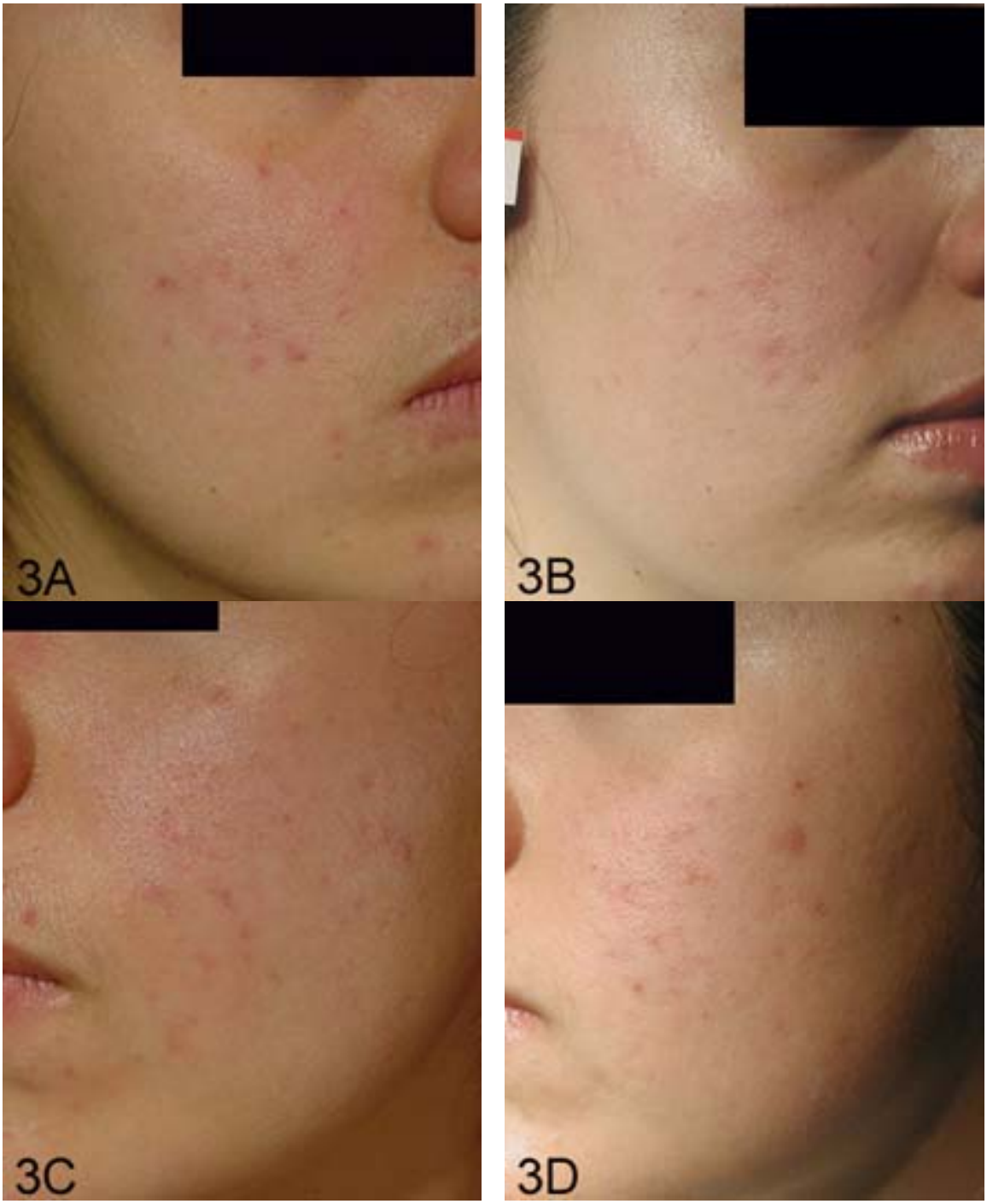

Figure 3. 18 year-old Latino female with acne vulgaris treated with CHARME twice daily. **3A.** Baseline. **3B.** After 8 weeks of therapy, a decrease in inflammatory acne lesions with minimal erythema is noted. **3C.** Same patient at baseline (control). **3D.** Control at 8 weeks. No improvement observed in acne lesion counts.

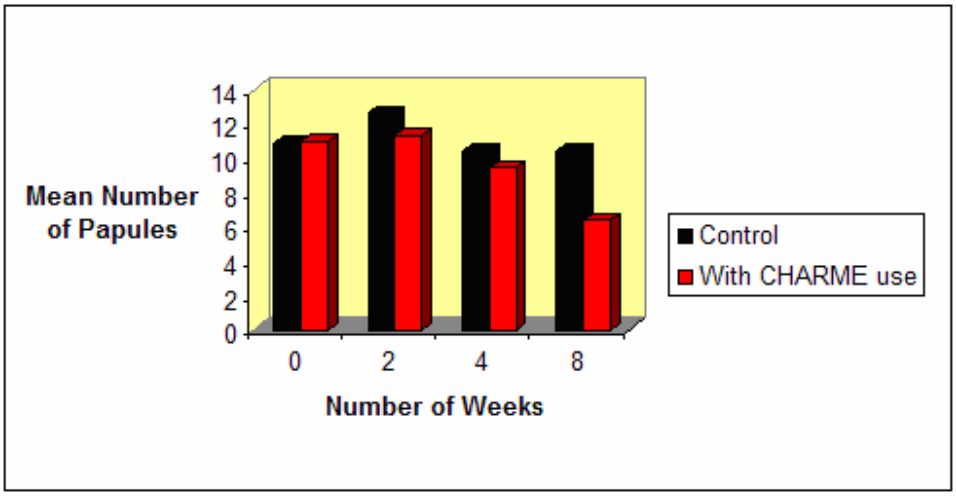

Figure 4. Graph comparing the number of papules over the 8-week treatment period with CHARME use and control. A greater reduction in the number of papules is noted with CHARME use compared to control.

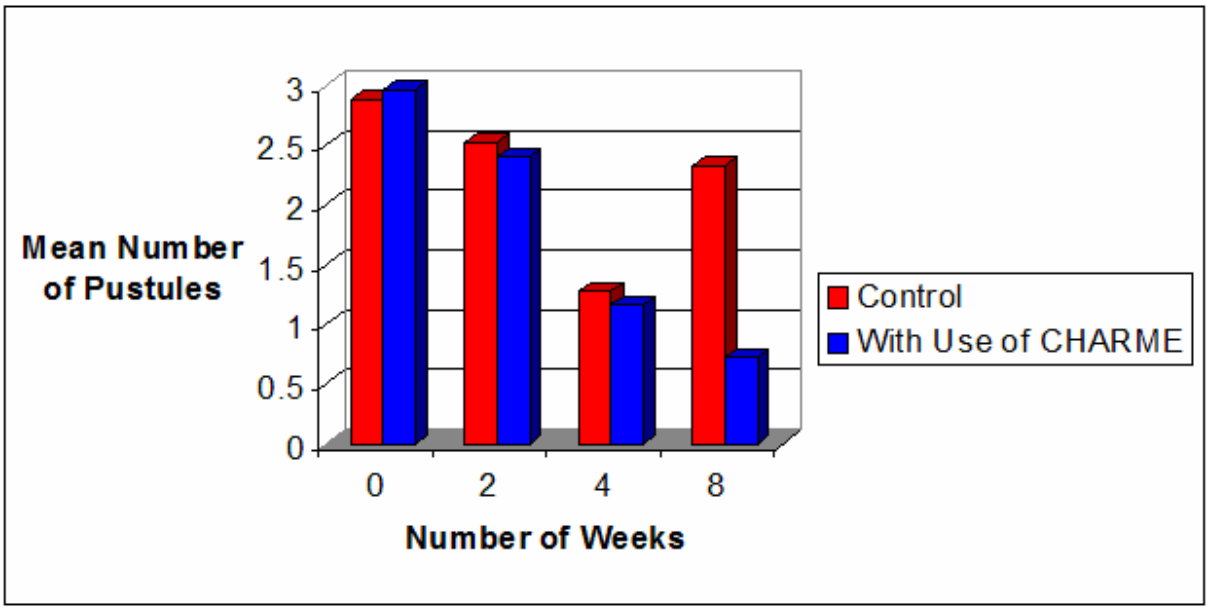

Figure 5. Graph comparing the number of pustules over the 8-week treatment period with CHARME use and control. A greater reduction in the number of pustules is noted with CHARME use compared to control.

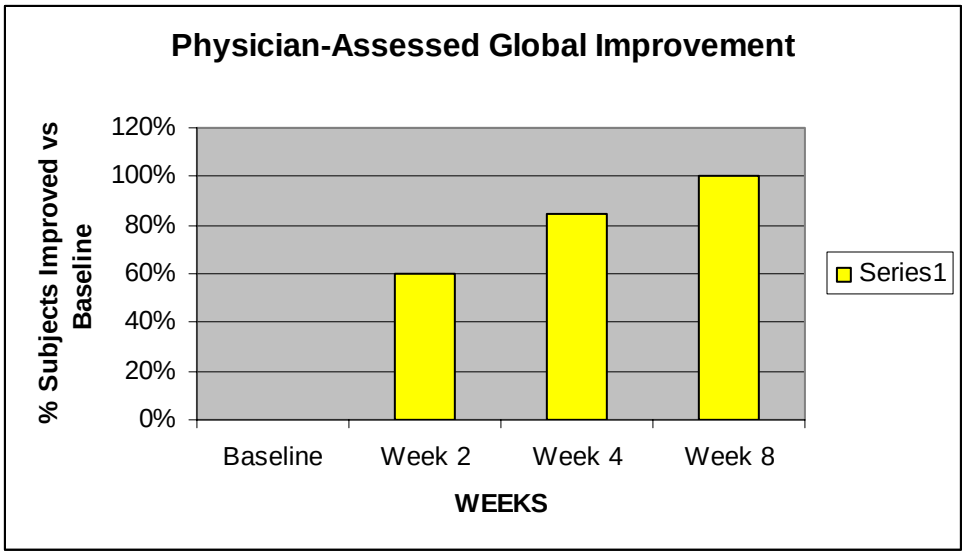

Figure 6. Physician evaluation of global improvement from baseline.

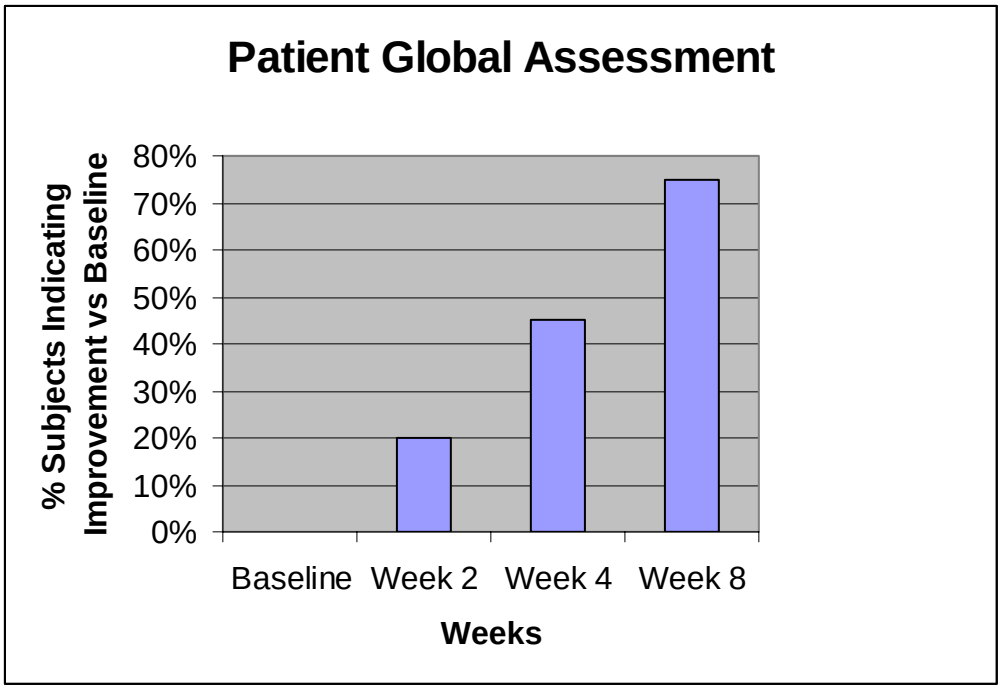

Figure 7. Patient self-assessment results—percentage of patients who indicated overall improvement in their acne from baseline to week 8.

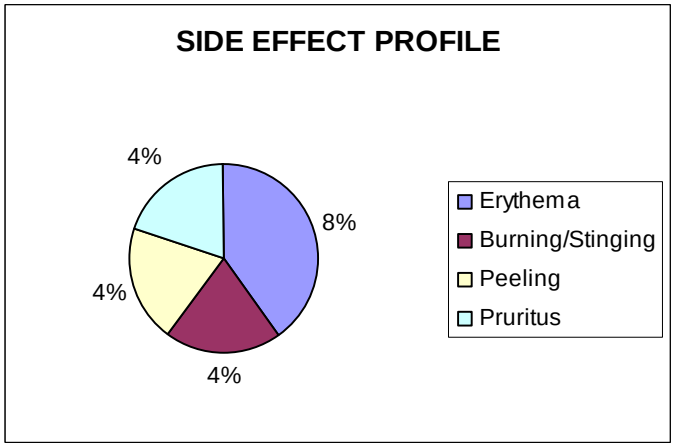

Figure 8. Percentage of cutaneous side-effects experienced with CHARME after 8 weeks of treatment.

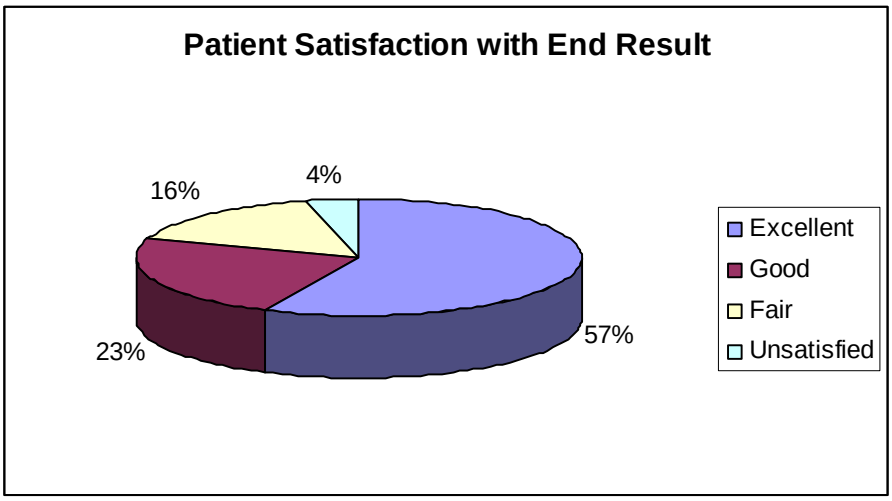

Figure 9. Patient satisfaction with the CHARME device after treatment period.

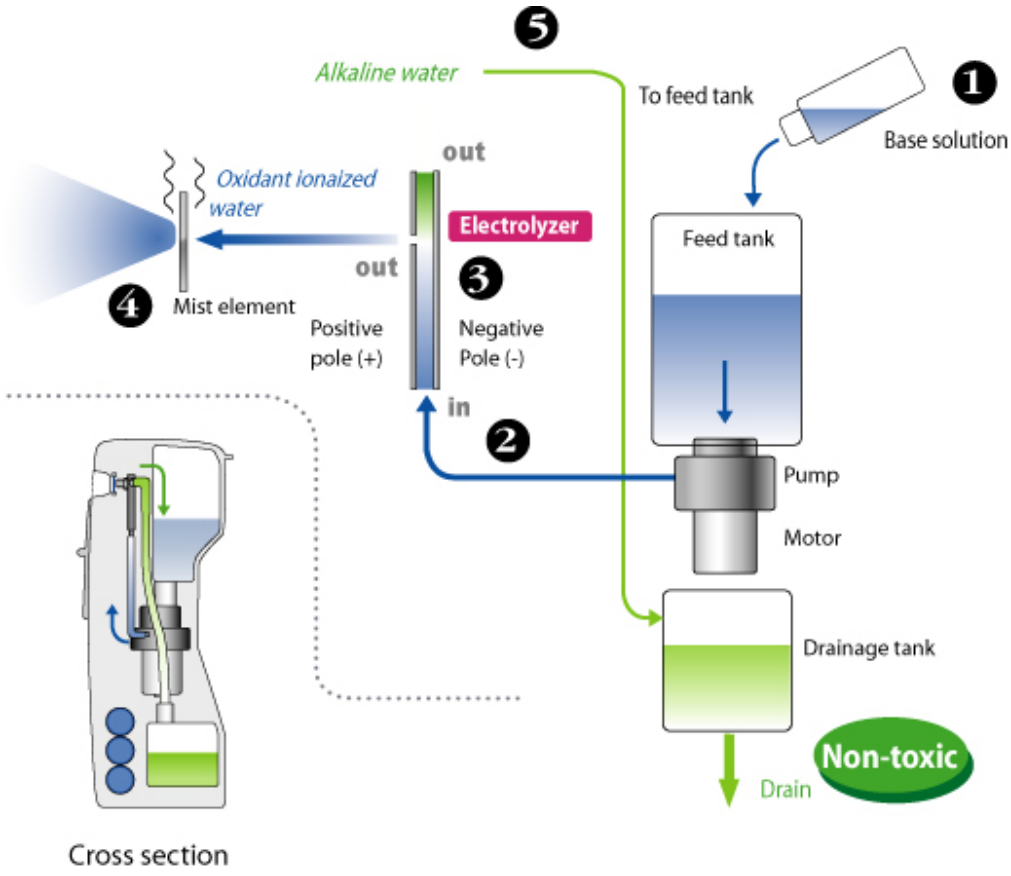

Figure 10. Diagram illustrating the process of electrolysis (steps 1-5). After the water-based sodium chloride solution (Base Solution) is introduced into the CHARME unit, the electrolysis process begins. Within seconds, electrolyzed oxidized water is emitted as a fine mist to the skin. Non-toxic alkaline solution is collected in the drainage tank and emptied after use.

TABLE 1

Anti-microbial effects of Low pH water in a laboratory setting

Bacteria	*Count prior to testing*	*5 sec.*	*10 sec.*	*30 sec.*
E.coli	3.94 mil	<100	<100	<100
S. aureus	12.5 mil	<100	<100	<100
S. pyogenes	8.95 mil	<100	<100	<100
P. aeruginousa	17.82 mil	<100	<100	<100
MRSA	11.24 mil	<100	<100	<100
Salmonella	13.80 mil	<100	<100	<100
Sporular sp.	11.40 mil	<100	<100	<100

Testing Agency: Food and Drug Safety Center, Japan *mil = million
Bacteria broth: Low pH acidic water = 1:100

REFERENCES

1. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. *J Am Acad Dermatol.* 1998;39:S34-7.
2. Stern RS. The prevalence of acne on the basis of physical examination. *J Am Acad Dermatol*. 1992;26:931-5.
3. Cunliffe WJ, Gould DJ. Prevalence of acne in late adolescence and in adults. *Br Med J.* 1979;1:1109-10.
4. Mallon E, Newton JN, Klassen A, *et al*. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. *Br J Dermatol.* 1999;140:672-6.
5. Koo J. The psychosocial impact of acne: patients' perceptions. *J Am Acad Dermatol.* 1995;32:S26-S30.
6. Lee W-L, Shalita AR, Suntharalingam K, Fikrig SM. Neutrophil chemotaxis by *Propionibacterium acnes* lipase and its inhibition. *Infect Immun.* 1982;35:71-78.
7. Allaker RP, Greenman J, Osborne RH. The production of inflammatory compounds by *Propionibacterium acnes* and other skin organisms. *Br J Dermatol.* 1987;117:175-183.
8. Toyoda M, Morohashi M. Pathogenesis of acne. *Med Electron Microsc.* 2001;34:29-40.
9. Strauss JS, Thiboutot DM. Diseases of the sebaceous glands. In: Freedberg IM, Einsen AZ, Wolff K, et al, eds. Fitzpatrick's Dermatology in General Medicine, 5th ed. New York, NY: McGraw-Hill; 1998:769-784.

10. Thiboutot D. Hormones and acne: pathophysiology, clinical evaluation, and therapies. *Semin Cutan Med Surg*. 2001;20:144-153.
11. Jenkinson DM, Elder HY, Montgomery I, Moss VA. Comparative studies of the ultrastructure of the sebaceous gland. *Tissue Cell.* 1985;17:683-698
12. Norris JFB, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. *Br J Dermatol.* 1988;118:651-659.
13. Webster GF. Inflammation in acne vulgaris. *J Am Acad Dermatol.* 1995;33:247-253.
14. Stewart ME. Sebaceous gland lipids. *Semin Dermatol.* 1992;11:100-105.
15. Suh DC, Okpara IR, Agnese WB, Toscani M. Application of pharmacoeconomics to formulary decision making in managed care organizations. *Am J Manag Care.* 2002;8:161-169.
16. Bergfeld WF. The evaluation and management of acne: economic considerations. *J Am Acad Dermatol.* 1995;32(5 pt 3):S52-S56.
17. Bershad SV. The modern age of acne of acne therapy: a review of current treatment options. *Mt Sinai J Med.* 2001;68:279-286.
18. Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatology.* 1998;196(1):119-125.
19. Soto P, Cunliffe W, Meynadier J, Roseeuw D. Efficacy and safety of lymecycline 300mg plus adalpene 0.1% gel versus lymecycline 300mg plus adapalene gel vehicle in subjects with acne vulgaris. In: Program and Abstracts of the 60th Annual Meeting of the American Academy of Dermatology; February 22-27, 2002; New Orleans, LA. Abstract P36.

20. Zouboulis CC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazerd F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamyin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. *Br J Dermatol.* 2000;143:498-505.
21. Czernielewski J, Loesche C, Poncet M. Efficacy and safety comparison of adapalene gel, 0.1% and clindamycin topical lotion 1% vs in the treatment of acne vulgaris. In: Program and Abstracts of the 60th Annual Meeting of the American Academy of Dermatology; February 22-27, 2002; New Orleans, LA. Abstract P33.
22. Dreno B, Reynaud A, Moyse D, Habert H, Richet H. Erythromycin-resistance of cutaneous bacterial flora in acne. *Eur J Dermatol.* 2001;11:549-553.
23. Leyden JJ. Therapy for acne vulgaris. *N Engl J Med.* 1997;336:1156-1162.
24. Gollnick H, Schramm M. Topical drug treatment in acne. *Dermatology.* 1998;196:119-125.
25. Johnson BA, Nunley JR. Topical therapy for acne vulgaris: how do you choose the best drug for each patient? *Postgrad Med.* 2000;107:69-70, 73-6, 79-80.
26. Ortonne JP. Oral Isotretinoin treatment policy. Do we all agree? *Dermatology.* 1997;195(suppl):34-37; discussion 38-40.
27. Meigel WN. How safe is oral isotretinoin? *Dermatology.* 1997;195(suppl):22-28; discussion 38-40.

28. Jacob Cl, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. *J Am Acad Dermatol.* 2001;45:109-117.

29. Solish N, Raman M, Pollack SV. Approaches to acne scarring, a review. *J Cut Med Surg.* 1998;2 (Suppl 3): 24-32.

30. Shiba A, Shiba K. The current situation of application in medicine. *Jpn Strong Electrolyzed Solution Handbook.* 1995:105-14.

31. Shiba A, Shiba K. *Strong Electrolyzed Solution Handbook.* Tokyo: Igaku Johosha, 1995:98-9.

32. Okuda R, Sasazaki H, Kanebira M, Okabe T, Abe S, Tagami H. Electron microscopical study of bactericidal action of high oxidation potential water. *Jpn J Conserv Dentistry.* 1994;37:755-65.

33. Otoguro K, Suzuki F, Akimaru Y, Iijima M, Yajima Y, Uebaba K. Hand disinfectant activities of two kinds of electrolyzed acid aqueous solution by Globe Juice Method. *Envir Toxicol Water Quality*. 1996;11:117-122.

34. Tanaka N, Fujisawa T, Daimon T, Fuhiwara K, Tanaka N, Yamamoto M, Abe T. The effect of electrolyzed strong acid aqueous solution on hemodialysis equipment. *Artif Organs.* 1999;23:1055-62.

35. Tanaka N, Yamamoto M, Daimon T, Fujiwara K, Fujisawa T, Tanaka N, Kakihara M, Nakano T, Ryu S, Abe T. The use of electrolyzed strong acid aqueous solutions in dialysis equipment. *Jpn J Clin Dialysis.* 1997;13:113-118.

36. Sakurai Y. Electrolyzed water and endoscopy disinfection. *Functional Water Symposium.* Yokohama, Japan, 1998:12-13.

37. Kiura, H., Sano, K., Morimatsu, S., Nakano, T., Morita, C., Yamaguchi, M., Maeda, T., Katsuoka, Y. *Journal of Microbiological Methods*. 2002; 49:285-293.
38. Kumon K. What is functional water? *Artif Organs.* 1997;21:2-4.
39. Tanaka N, Fujisawa T, Daimon T, Fujiwara M, Yamamoto M, Abe T. The cleaning and disinfecting of hemodialysis equipment using electrolyzed strong acid aqueous solution. *Artif Organs.* 1999;23:303-309.
40. Shirahata S, Kabayma S, Nakano M, et al. Electrolyzed-reduced water scavenges active oxygen species and protects DNA from oxidative damage. *Biochem Biophys Res Commun.* 1997;234:269-274.
41. Hajime N., Inaba, H. Effectiveness of Electrolyzed Oxidized Water Irrigation in a Burn-Wound Infection Model. *The Journal of Trauma Injury, Infection, and Critical Care*. 2000; 49:511-514.
42. Shimizu Y, Sugawara H. Virucidal and bactericidal effects of electrolyzed oxidizing water: comparison of disinfectant effect with electrolyzed oxidizing water and hypochlorous acid. *Jpn J Oral Biol.* 1996;38:564-571.
43. Hotta K. What is the main sterilizing component? In: Kenkyukai W, ed. *The Basic Knowledge of ESAAS.* Tokyo: Ohmsha, 1997:26-31.
44. Kohno M. Electrolytic water as a solution. In: Kenkyukai W, ed. *The Basic Knowledge of ESAAS.* Tokyo: Ohmsha. 1997:40-44.
45. Inoue Y, Endo S, Kondo K, Ito H, Omori H, Saito K,. Trial of electrolyzed strong acid aqueous solution lavage in the treatment of peritonitis and intraperitoneal abscess. *Artif Organs*. 1997;21:28-31.

46. Sekiya S, Ohmori K, Harii K. Treatment of infectious skin defects or ulcers with electrolyzed strong acid aqueous solution. *Artif Organs.* 1997;21:32-38.

47. Wessels F, Anderson AN, Kropman K. The cost-effectiveness of isotretinoin in the treatment of acne. Part 2, A chronic medication plan profiling study. *S Afr Med J.* 1000;39(7 pt 2):785-790.

48. Leyden J. Are 2 combined antimicrobial mechanisms better than 1 for the treatment of acne vulgaris? Clinical and antimicrobial results of a topical combination product containing 1% clindamycin and 5% benzoyl peroxide. *Cutis.* 2001;67(suppl):5-7.

49. Meynadier J, Allrezal M. Systemic antibiotics for acne. *Dermatology.* 1998;196:135-139.

50. Vibramycin [package insert]. New York, NY: Pfizer Inc; 1993.

51. Greenwald RA, Golub LM. Preface: nonantibiotic properties of tetracyclines. *Adv Dent Res.* 1998;12:1.

52. Layton AM, Cunliffe WJ. Phototoxic eruptions due to doxycycline: a dose-related phenomenon. *Clin Exp Dermatol.* 1993;18:425-427.

53. Espersen F. Resistance to antibiotics used in dermatological practice. *Bt J Dermatol.* 1998;139(suppl):4-8.

54. Sturkenboom MC, Meler CR, Jick H, Stricker BH. Minocycline and lupus-like syndrome in acne patients. *Arch Intern Med.* 1999;159:493-497.

55. MacNeil M, Haase DA, Tremaine R, Marrie TJ. Fever, lymphadenopathy, eosinophilia, lymphocytosis, hepatitis and dermatitis: a severe adverse reaction to minocycline. *J Am Acad Dermatol.* 1997;36(2 pt 2):347-350.

56. Somech R, Arav-Boger R, Assia A, Spirer Z, Jurgenson U. Complications of minocycline therapy for acne vulgaris: case reports and review of the literature. *Pediatr Dermatol.* 1999;16:469-72.

57. Leyden JJ. The evolving role of *Propionibacterium acnes* in acne. *Semin Cutan Med Surg.* 2001;20:139-143.