Drugs 2004; 64 (21): 2389-2397
0012-6667/04/0021-2389/$34.00/0

Topical Antibacterial Therapy for Acne Vulgaris

Brigitte Dreno

Department of Dermatology, Hotel Dieu, Nantes, France

Contents

Abstract

Topical antibiotics and benzoyl peroxide, are the two main topical antibacterial treatments indicated for mild-to-moderate acne vulgaris. Topical antibiotics act both as antibacterial agents suppressing *Propionibacterium acnes* in the sebaceous follicle and as anti-inflammatory agents. Benzoyl peroxide is a powerful antimicrobial agent that rapidly destroys both bacterial organisms and yeasts. Topical clindamycin and erythromycin have been proven to be effective against inflammatory acne vulgaris in concentrations of 1–4% with or without the addition of zinc. However, none of the antibacterials tested was more effective than benzoyl peroxide, which also has the advantage of not being associated with antimicrobial resistance.

Topical antibacterial therapy should be discontinued once improvement is observed. If no improvement is observed within 6–8 weeks, the agent should be discontinued and a therapeutic switch considered. The primary limitation of benzoyl peroxide for some acne vulgaris patients is cutaneous irritation or dryness.

Antibacterial therapy can be used in combination with other agents. Combining topical antibiotics and topical retinoids may enhance the efficacy, since the retinoid will improve the penetration of the antibiotic. Combining a topical antibiotic with benzoyl peroxide may increase the bactericidal effect of the antibiotic and reduce the potential for bacterial resistance. Topical and oral antibacterials should not be used in combination for the treatment of acne vulgaris, since this association may increase the risk of bacterial resistance.

In recent years, research has led to a greater understanding of the pathogenesis of acne vulgaris. The pilosebaceous follicle is the target organ in acne vulgaris, explaining the distribution of acne vulgaris primarily on the face, chest and back, areas with the greatest concentration of pilosebaceous glands. The most notable pathophysiological factors that influence the development of acne vulgaris are increased sebum production by the sebaceous gland, ductal hypercornification of the pilosebaceous follicle and *Propionibacterium acnes* colonisation of duct-inducing local inflammation and immune response.[1]

P. acnes is the main target of antibacterial treatment of acne vulgaris. The obstruction of the follicular canal by abnormal desquamation of the follicular epithelium retains sebum within, thus favouring the proliferation of *P. acnes*. The exact role of *P. acnes* in the development of acne vulgaris lesions is still a point of discussion. Indeed, while it has been considered to be an infectious agent for a long time, it seems, according to the recent data, that it is more likely to act by producing different inflammatory substances (lipase, chemotactic factor, etc.) that induce the development of inflammatory lesions.[1,2] There is a correlation between the reduction of *P. acnes* and the clinical improvement of acne vulgaris. This reduction in *P. acnes* is associated with a reduction in pro-inflammatory mediators. The intensity of host response to inflammatory stimuli most likely explains the variations in the intensity of inflammatory acne vulgaris. Certain cytokines, such as tumour necrosis factor-α and interferon-γ, may be inflammatory triggers, and whether neuroinflammatory mediators play an additional role is currently under debate. Moreover, very recently it has been shown that immediate immunity may be implicated in inflammatory reactions in acne vulgaris through toll-like receptors (TLR2, TLR4), which are receptors expressed by keratinocytes and which may be activated directly by bacterial antigens such as *P. acnes* inducing an immediate production of inflammatory cytokines by the activated keratinocytes.[3]

This recent information concerning the pathophysiology of acne vulgaris is important for the dermatologist to consider in the use of topical antibacterial treatment for patients with acne vulgaris, especially in the context of the bacterial resistance that is associated with topical antibacterials today.[4]

1. Antibacterial Therapy

The two main antibacterial treatments in acne vulgaris are topical antibiotics and benzoyl peroxide.

1.1 Topical Antibiotics

Clindamycin and erythromycin are the most popular topical antibacterials for acne vulgaris.[5] Topical tetracycline is used less often and very few use meclocycline.[6] Clindamycin and erythromycin have proven to be effective against inflammatory acne vulgaris in topical form in concentrations of 1–4% with or without the addition of zinc.[4,7] Re-

cently, a liposome-encapsulated 1% clindamycin preparation has been proposed. On the basis of a clinical trial it may be concluded that liposome-encapsulated 1% clindamycin solution is therapeutically superior over conventional 1% clindamycin solution in the treatment of acne vulgaris.[8]

1.2 Benzoyl Peroxide

Benzoyl peroxide is available in a variety of formulations and in concentrations ranging from 1% to 10%.[9-11]

Benzoyl peroxide is a well tolerated and effective agent for treating acne vulgaris, and has an efficacy that is maintained over years of use.[12]

Gel formulations of benzoyl peroxide may be preferred over creams and lotions because of better stability and more consistent release of the active ingredient. Benzoyl peroxide soaps may be considered for adolescent boys, both to enhance compliance (the soap may be conveniently applied in the shower) and to cover large skin areas such as the chest and back. As with all topical medications, it should be applied to the entire affected area, usually in the morning and the evening, and not only to the visible lesions.

2. Mechanisms of Action

2.1 Topical Antibiotics

Topical antibiotics have both anti-inflammatory and antibacterial mechanisms.

2.1.1 Anti-inflammatory Mechanisms

The anti-inflammatory mechanisms are:

- suppression of leucocyte chemotaxis;
- a reduction in the number of *P. acnes*;
- a decrease in the percentage of proinflammatory free fatty acids in skin surface in the surface lipids. This activity is probably due to a direct anti-lipase activity and a decrease of lipase produced by *P. acnes.*

These three mechanisms are all shown equally by erythromycin, clindamycin and tetracycline.[13] However, inhibition of lipase production by *P. acnes in vitro* at a concentration lower than the minimum inhibitory concentration has only been shown with erythromycin and tetracycline.[14]

2.1.2 Antibacterial Mechanism

Very little information is given in the literature concerning the bactericidal effect of the topical antibiotics on *P. acnes*, and the published research suggests that both topical erythromycin and cindamycin have a moderate direct effect on *P. acnes*, not significantly reducing the number of surface and follicular bacteria.[15]

If the point that antibacterials do not significantly reduce the number of surface and follicular bacteria is confirmed in the future, it would indicate that current topical antibiotics probably act more by an anti-inflammatory than an antibacterial activity on these lesions.[1,16] It means that topical antibiotics would act on inflammatory lesions by inhibiting inflammatory substances produced by *P. acnes* (lipase, metalloproteases, chemotactic factors, etc.).

2.2 Benzoyl Peroxide

Benzoyl peroxide also acts by anti-inflammatory and antibacterial mechanisms.

2.2.1 Anti-inflammatory Mechanism

Benzoyl peroxide inhibits the production of reactive oxygen species from human neutrophils.[17,18] The exact mechanisms of this inhibition are still not well known. *In vitro*, it slightly inhibits protein kinase C and has no modulating effect on calmodulin, the two regulators of reactive oxygen species. To date, no activity of benzoyl peroxide on the sebaceous gland has been demonstrated and it does not modulate the differentiation or proliferation of keratinocytes of the pilosebaceous epithelium.[1]

2.2.2 Antibacterial Mechanism

Benzoyl peroxide has a rapid bacteriostatic – possibly bactericidal – action. The literature review performed by Eady et al.[6] showed that none of the topical antibiotics tested was more effective than benzoyl peroxide. However, it should be noted that reduction in *P. acnes* has not been proven to be always related to clinical effectiveness. Benzoyl peroxide also has the advantage of not being associated with bacterial resistance. Benzoyl peroxide in

combination with erythromycin or clindamycin has been shown to be more effective and better tolerated than benzoyl peroxide alone.[10,19]

The predominant activity of benzoyl peroxide on *P. acnes*, whether is anti-inflammatory or antibacterial, has not been determined to date.

3. Clinical Trials of Acne Vulgaris Treatments

A lot of clinical trials on the efficacy of topical antibiotics or benzoyl peroxide have been performed. These included:

- placebo-controlled trials
- comparative studies between two different topical antibiotics
- comparative studies between a topical antibiotic and benzoyl peroxide
- comparative studies between topical antibiotics and oral antibacterials
- comparative studies with combined therapy.

Both benzoyl peroxide and topical antibiotics act essentially on inflammatory lesions. However, the comparisons between the different clinical trials remain difficult. Indeed, there are considerable variations between the trials in patient profile and criteria of evaluation.

3.1 Topical Antibiotics

Eady et al.[6] in 1990 and Toyoda and Morohashi[15] in 1998 reported a critical evaluation of topical antibiotics in acne vulgaris.

On the basis of these two main reviews and more recent data, it appears that erythromycin is the most effective topical antibiotic on inflammatory acne vulgaris lesions (94% improvement with erythromycin, 82% with clindamycin and 70% with tetracycline). No significant difference was noted between 1% and 4% erythromycin.

In summary, erythromycin and clindamycin appear to be more effective than placebo, although the conclusion is similar, but a little less definite, with tetracycline. Concerning the non-inflammatory lesions and the topical antibiotic used (tetracycline, clindamycin or erythromycin), the percentage reduction of retentional lesions remained low (<30%).

3.2 Benzoyl Peroxide

Benzoyl peroxide has been the most widely used topical agent for acne vulgaris since the 1960s. It has an antibacterial activity and, like topical erythromycin, benzoyl peroxide has a main activity on inflammatory lesions (papules and pustules).[20]

Besides being antibacterial, benzoyl peroxide also functions as a peeling agent, with a low comedolytic activity (<20%) on retentional lesions (closed and opened comedones). Indeed, few studies have shown that benzoyl peroxide is slightly more efficient on retentional lesions.[21,22] However, a sebosupressive activity has not been shown. Topical 5% benzoyl peroxide (no study with 10%) has been shown to be more effective than topical antibiotics on noninflammatory lesions.[23] Moreover, a 6% benzoyl peroxide preparation suppressed the follicular population of *P. acnes* more rapidly and to a greater degree than topical antibiotics such as clindamycin.[24]

3.3 Topical Antibiotics and Oral Tetracyclines

Several studies have been performed comparing oral tetracycline 500–1000 mg/day with topical antibiotics for 12 weeks.[13,25-28] No significant differences were noted between tetracycline and topical antibiotics on the reduction of inflammatory lesions over 12 weeks. However, these results have to be interpreted with caution; indeed, the dosages of tetracycline used were lower than those generally used in clinical practice.

3.4 Combination Therapy

Table I provides an overview of combined and single agent topical therapies and their associated activities.

3.4.1 Zinc and Erythromycin

The combination of erythromycin with zinc could increase the spectrum of activity on retentional lesions and decrease the percentage of resistant strains compared with erythromycin alone. It has

Table I. Combined and single agent topical therapies for acne vulgaris and their associated activities

Topical therapy	Comedolytic activity	Sebosuppressive activity	Antimicrobial activity	Anti-inflammatory activity	Prevalence of resistant *Propionibacterium acnes* strains
ERY	−	−	++	+	High
CLI	−	−	++	+	High
TET	−	−	++	++	High
BP	+	−	+++	+	No
TRE	++	−	+	−	No
ADA	++	−	+	++	No
ISO	++	−	+	+	No
ERY or CLI + BP	−	−	+++	++	Low
ERY or CLI + TRE or ISO	++	−	++	+	Low
ERY or CLI + ADA	++	−	++	++	Low
ERY + Zn	+	−	++	++	Low

ADA = adapalene; **BP** = benzoyl peroxide; **CLI** = clindamycin; **ERY** = erythromycin; **ISO** = isotretinoin; **TET** = tetracycline; **TRE** = tretinoin; **Zn** = zinc; **–** indicates none; **+** indicates weak; **++** indicates moderate; **+++** indicates strong.

been shown *in vitro* that *P. acne* strains are inhibited by zinc at concentrations ≤512 μg/mL.[29] Holland et al.[7] showed that the growth of erythromycin-resistant strains of *P. acne* is inhibited by the addition of zinc 300 μg/mL to erythromycin 1000 μg/mL. Whereas Bojar et al.[30] found no additional efficacy of zinc used with erythromycin on inflammatory acne vulgaris lesions *in vivo*, Habbema et al.,[31] Schachner et al.[32] and Feucht et al.[33] showed that the combination of zinc and erythromycin was more effective than erythromycin alone on the course of inflammatory acne vulgaris lesions.

3.4.2 Retinoids and Topical Antibiotics

Retinoids have both comedolytic and anti-inflammatory activities. The comedolytic activity is related to a normalisation of the desquamation of the follicular epithelium. Thus, combined therapy increases the anti-inflammatory activity of the topical antibiotic, decreases the risk of resistance and increases the spectrum of activity of antibacterials to the retentional lesions. Moreover, tretinoin increases the penetration of topical antibiotics used in conjunction with it. Comparative trials have been performed between topical antibiotics alone and combined therapy (topical antibiotic and retinoid), showing a faster effect with the combined therapy both on inflammatory and retentional lesions. Both clindamycin and erythromycin combined with a topical retinoid (0.025% tretinoin or isotretinoin) are more effective than when used alone. The tolerability is good; the addition of a topical antibiotic may even decrease the irritation caused by the retinoid.[34-36] However, a multicentre, randomised, double-blind, parallel-group study comparing the effectiveness of 3% erythromycin/5% benzoyl peroxide versus 0.025% tretinoin/4% erythromycin, each applied twice daily in patients with moderate acne vulgaris for 12 weeks, reported that the number of papules, pustules and comedones was reduced in both treatment groups at week 12, and the reductions were not significantly different between the two treatments. The 3% erythromycin/5% benzoyl peroxide combination demonstrated significantly greater reduction of erythema and scaling compared with 0.025% tretinoin/4% erythromycin.[37]

3.4.3 Benzoyl Peroxide and Topical Antibiotics

Benzoyl peroxide and topical antibiotics can be used separately (one product in the morning, the other one in the evening) or in a same product. In either case, the randomised studies show that the combined therapy gives the lowest severity grade throughout the evaluation period. Erythromycin/benzoyl peroxide was the first combined therapy used. This formulation appears to be more effective than each product alone, but the difference is more significant with erythromycin alone than with benzoyl peroxide.[38]

Recently, three independent randomised trials have been performed with a combination of 1% clindamycin/5% benzoyl peroxide gel formulation in a total of 1250 patients with mild-to-moderate acne vulgaris.[39-41] The results indicated that the benzoyl peroxide/clindamycin combination product was an effective treatment for reducing the inflammatory lesions, but has only a minor effect on non-inflammatory lesions of acne vulgaris. Moreover, at the bacteriological level, the total *P. acnes* count ($p = 0.002$) and the clindamycin-resistant *P. acnes* count ($p = 0.018$) appeared significantly reduced after 16 weeks of treatment with combination gel compared with clindamycin monotherapy. These reductions in total *P. acnes* and clindamycin-resistant *P. acnes* counts correlated with reductions in total acne vulgaris lesions.[42]

4. Adverse Effects

4.1 Topical Antibiotics

The tolerance of topical antibiotics is generally excellent. The main adverse effects are irritation with erythema, peeling, itching, dryness and burning. Pseudomembranous colitis is rare, but has been observed after topical treatment with clindamycin hydrochloride and clindamycin phosphate.[43,44] This good tolerability explains why topical antibiotics are often prescribed even in summer.

4.2 Benzoyl Peroxide

The primary limitation of benzoyl peroxide for some acne vulgaris patients is concentration-dependent cutaneous irritation or dryness and bleaching of hair, clothes and bed linens. Benzoyl peroxide can induce an irritant dermatitis with erythema, scaling and itching. These adverse effects occur primarily within the first few days of treatment and subside with continued use.[45,46]

Antibacterial/retinoid combinations, which have the potential to increase the spectrum of activity of topical treatment on acne lesions, are often associated with more adverse effects (erythema, scaling and itching).

5. Bacterial Resistance

For the last few years, there has been an increased frequency of the number of patients carrying *P. acnes* and *Staphylococcus epidermidis* resistant to current topical antibiotics, which have been used for more than 30 years.[47] This resistance raises two questions.

1. What are the potential risks at the clinical level for the patients?

2. Does the presence of these resistant strains decrease the effectiveness of topical antibiotics largely used today to treat acne vulgaris?

As yet, no formal conclusion has been given to these two questions. This is particularly related to the fact that the antibiotics can act on the inflammatory lesions of acne vulgaris by two different mechanisms: anti-inflammatory and antibacterial. To date, it is still not clear which is the prevalent mechanism in their effectiveness. A recent survey, conducted throughout Europe, showed that at least 50% of acne vulgaris patients are colonised by erythromycin- and clindamycin-resistant strains of *P. acnes*.[48] Resistance appears to emerge through either selection of pre-existing resistant bacterial strains, or through *de novo* acquisition of a resistant phenotype. There is cross resistance between erythromycin and clindamycin. Two types of mutations (ribosomal RNA 16S and 23S) have been found, conferring to the strains a cross resistance with the macrolides, lincosamides and type B streptogramins.[49] The duration of treatment required before resistance emerges varies greatly between patients, but the longer the duration of treatment, the more likely antibacterial-resistant *P. acnes* will emerge, and courses of 6 months are highly likely to result in resistance. In France, a study of 40 acne vulgaris patients showed a prevalence of 95% of strains of *S. epidermidis* and 52% of *P. acne* resistant to erythromycin.[29]

Moreover, at the clinical level, there are three studies showing a recognised correlation between the presence of antibacterial-resistant *P. acnes* and clinical response to treatment with topical antibiotics.[47,50,51]

The potential risks of using topical erythromycin and clindamycin are essentially related to the transfer of resistance to other bacteria, specifically *Streptococcus* spp. and *S. aureus*. The study by Mills et al.[47] demonstrated that topical erythromycin increased the frequency of erythromycin-resistant *S. aureus* at the nares.[47] Further studies are necessary to confirm or discount this risk.

Thus, from these studies, it appears that bacterial resistance can be considered as a possible contributory factor to, or possible cause of, therapeutic failure. In addition, resistance to topical antibiotics may induce *de novo* resistance to these antibiotics in other commensally present bacteria (e.g. staphylococci), which often develop resistance much more quickly than in *P. acnes* and may be a potential risk for the patient.

Furthermore, antibacterial-resistant strains can be transmitted between individuals, and studies have shown that 41–85.7% of untreated close contacts of acne vulgaris patients having long-term topical antibiotic treatment harbour erythromycin-resistant strains of *P. acnes*.[52] Even dermatologists may be colonised by resistant strains compared with non-dermatologist physicians.[53] Resistant strains can be reduced at the sites of application by using the topical antibacterial agent benzoyl peroxide. Oral antibacterials should not be combined with topical antibiotics. Indeed, this may increase the risk of *P. acnes* resistance and provides no additive benefit. However, no single available agent will fully eradicate antibacterial-resistant *P. acnes*.

6. Other Topical Antibacterials

Meclocycline is an oxytetracycline derivative available as a 1% cream. One study has shown a significant efficacy of meclocycline on inflammatory lesions compared with vehicle.[54]

Nadifloxacin is a synthetic fluoroquinolone derivative. A double-blind, vehicle-controlled trial showed that nadifloxacin is significantly superior to control in the decrease of acne vulgaris lesions and in the number of *P. acnes* in the follicle, with a minimum inhibitory concentration lower than that of tetracycline and minocycline.[55] The incidence of resistant strains is expected to be low, but the available data at the moment are limited to one study.[56]

Azelaic acid is a 9-dicarbonic acid which targets follicular keratinisation and *P. acnes*. It is available in a 20% cream formulation. Compared with benzoyl peroxide, its efficacy is mainly on retentional lesions. Its activity on inflammatory lesions is slower than benzoyl peroxide but appears similar after 12–16 weeks of treatment.[57] No report of *P. acnes* resistance to azelaic acid has been reported.

7. Recommendations

From the data discussed in this article, the following recommendations may be proposed concerning the use of topical antibiotics in acne vulgaris.

- Do not use topical antibiotics where other topical acne vulgaris treatments (retinoids, benzoyl peroxide) can be expected to bring the same benefit.
- Do not use a topical antibiotic alone; rather, use in a combined therapy with retinoids or benzoyl peroxide.
- Do not combine topical and systemic antibacterials.
- Stop topical antibiotic therapy when there is no further improvement or the improvement is only slight.
- Try to avoid continuing topical antibiotics for a long period (6–8 weeks into treatment might be one appropriate timepoint at which to assess response).
- Check patient's compliance with treatment.

Topical benzoyl peroxide has been shown to be active against fully sensitive and resistant strains of *P. acnes.* Therefore, this agent reduces the likelihood of emerging antibacterial-resistant *P. acnes* and reduces the number of resistant bacteria *in situ*.

In patients in whom bacterial resistance is suspected, topical antibiotics are often simply discontinued. However, ideally, such patients should be managed by first swabbing and culturing to verify the presence of resistant strains and then using non-antibiotic therapies such as topical benzoyl peroxide, topical or systemic retinoids, hormonal therapies or systemic zinc salts.

8. Conclusion

Topical antibacterial treatments have both antibacterial and anti-inflammatory activities and, at the moment, which activity is predominant on inflammatory lesions remains to be determined. Topical antibacterials are effective on mild-to-moderate acne vulgaris.

The adverse effects of these topical antibacterials are minor; the main problem remains the development of resistant strains (absent with benzoyl peroxide). Thus, topical antibiotics should not be prescribed alone, but always in combination (with topical retinoid, benzoyl peroxide, or topical or systemic zinc). Finally, the topical antibacterial products exert little activity on non-inflammatory lesions. In any case, it is important to have a standardisation of acne vulgaris clinical trials in the future to allow better evaluation of the different topical products.

Acknowledgements

The author has provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

References

1. Gollnick H. Current concepts of the pathogenesis of acne: implications for drug treatment. Drugs 2003; 63 (15): 1579-96
2. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. J Am Acad Dermatol 2003; 49 (1 Suppl.): S1-2
3. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. J Immunol 2002; 169: 1535-41
4. Kurokawa I, Nishijima S, Kawabata S. Antimicrobial susceptibility of *Propionibacterium acnes* isolated from acne vulgaris. Eur J Dermatol 1999; 9: 25-8
5. Johnson BA, Nunley JR. Topical therapy for acne vulgaris: how do you choose the best drug for each patient? Postgrad Med 2000; 107: 69-80
6. Eady EA, Cove JH, Joanes DN, et al. Topical antibiotics for the treatment of acne vulgaris: a critical evaluation of the literature on their clinical benefit and comparative efficacy. J Dermatol Treat 1990; 1: 215-26
7. Holland KT, Bojar RA, Cunliffe WJ, et al. The effect of zinc and erythromycin on the growth of erythromycin-resistant and erythromycin-sensitive isolates of *Propionibacterium acnes*: an *in-vitro* study. Br J Dermatol 1992; 126: 505-9
8. Honzak L, Sentjurc M. Development of liposome encapsulated clindamycin for treatment of acne vulgaris. Pflugers Arch 2000; 440 (5 Suppl.): R44-5
9. Gollnick H, Schramm M. Topical drug treatment in acne. Dermatology 1998; 196: 119-25
10. 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: introduction. Cutis 2001; 67 (2 Suppl.): 5-7
11. Patel VB, Misra AN, Marfatia YS. Preparation and comparative clinical evaluation of liposomal gel of benzoyl peroxide for acne. Drug Dev Ind Pharm 2001; 27: 863-9
12. Plewig G, Kligman AM. Acne and rosacea. 3rd ed. New York: Springer-Verlag, 2000
13. Rapaport M, Madli Puhvel S, Reinsmer RM. Evaluation of topical erythromycin and oral tetracycline in acne vulgaris. Cutis 1982; 30: 122-35
14. Eady EA, Holland KT, Cunliffe WJ, et al. Propionibacterium levels in patients with and without acne vulgaris. J Invest Dermatol 1975; 65: 382-4
15. Toyoda M, Morohashi M. An overview of topical antibiotics for acne treatment. Dermatology 1998; 196: 130-4
16. Akhavan A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. Am J Clin Dermatol 2003; 4: 473-92
17. Hegemann L, Toso SM, Kitay K, et al. Anti-inflammatory actions of benzoyl peroxide: effects on the generation of reactive oxygen species by leucocytes and the activity of protein kinase C and calmodulin. Br J Dermatol 1994; 130: 569-75
18. Valacchi G, Rimbach G, Saliou C, et al. Effect of benzoyl peroxide on antioxidant status, NF-kappaB activity and interleukin-1alpha gene expression in human keratinocytes. Toxicology 2001; 165: 225-34
19. Basak PY, Gultekin F, Kilinc I, et al. The effect of benzoyl peroxide and benzoyl peroxide/erythromycin combination on the antioxidative defence system in papulopustular acne. Eur J Dermatol 2002; 12: 53-7
20. Burke B, Eady EA, Cunliffe WJ. Benzoyl peroxide versus topical erythromycin in the treatment of acne vulgaris. Br J Dermatol 1983; 108: 199-204
21. Chalker DK, Shalila A, Smith JG, et al. A double blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. J Am Acad Dermatol 1983; 9: 933-6
22. Gans EH, Kligman AM. Comparative efficacy of clindamycin and benzoyl peroxide for *in vivo* suppression of *Propionibacterium acnes*. J Dermatolog Treat 2002; 13: 107-10
23. Swinyer LJ, Baker MD, Swinyer TA, et al. A comparative study of benzoyl peroxide and clindamycin phosphate for treating acne vulgaris. Br J Dermatol 1988; 119: 615-22
24. Burkhart CG, Butcher C, Burkhart CN, et al. Effects of benzoyl peroxide on lipogenesis in sebaceous glands using an animal model. J Cutan Med Surg 2000; 4: 138-41
25. 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: 50-3
26. Katsambas A, Towarky AA, Stratigos J. Topical clindamycin phosphate compared with oral tetracycline in the treatment of acne vulgaris. Br J Dermatol 1987; 116: 387-91
27. Burton J and the Dermatology Research Group. A placebo-controlled study to evaluate the efficacy of topical tetracycline and oral tetracycline in the treatment of mild to moderate acne. J Int Med Res 1990; 18: 94-103
28. Braathen LS. Topical clindamycin versus oral tetracyclines and placebo in acne vulgaris. Scand J Infect Dis 1984; 43: 71-5

29. Dreno B, Reynaud A, Moyse D, et al. Erythromycin-resistance of cutaneous bacterial flora in acne. Eur J Dermatol 2001; 11: 549-53

30. Bojar RA, Eady EA, Jones CE, et al. Inhibition of erythromycin-resistant proponibacteria on the skin of acne patients by topical erythromycin with and without zinc. Br J Dermatol 1994; 130: 329-33

31. Habbema L, Koopmans B, Menke HE, et al. A 4% erythromycin and zinc combination (Zineryt) versus 2% erythromycin (Eryderm) in acne vulgaris: a randomized, double-blind comparative study. Br J Dermatol 1989; 121: 497-502

32. Schachner L, Pestana A, Kittles C. A clinical trial comparing the safety and efficacy of a topical erythromycin-zinc formulation with a topical clindamycin formulation. J Am Acad Dermatol 1990; 22 (3): 489-95

33. Feucht CL, Allen BS, Chalker DK, et al. Topical erythromycin with zinc in acne: a double-blind controlled study. J Am Acad Dermatol 1980; 3: 483-91

34. Zouboulis CC, Derumeaux L, Decroix J, et al. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. Br J Dermatol 2000; 143: 498-505

35. Glass D, Boorman GC, Stables GI, et al. A placebo-controlled clinical trial to compare a gel containing a combination of isotretinoin (0.05%) and erythromycin (2%) with gels containing isotretinoin (0.05%) or erythromycin (2%) alone in the topical treatment of acne vulgaris. Dermatology 1999; 199: 242-7

36. Richter JR, Forstrom LR, Kiistala UO, et al. Efficacy of the fixed 1.2% clindamycin phosphate, 0.025% tretinoin gel formulation (Velac) and a proprietary 0.025% tretinoin gel formulation (Aberela) in the topical control of facial acne. J Eur Acad Dermatol Venereol 1998; 11: 227-33

37. Gupta AK, Lynde CW, Kunynetz RA, et al. A randomized, double-blind, multicenter, parallel group study to compare relative efficacies of the topical gels 3% erythromycin/5% benzoyl peroxide and 0.025% tretinoin/erythromycin 4% in the treatment of moderate acne vulgaris of the face. J Cutan Med Surg 2003; 7: 31-7

38. Chalker DK, Shalita A, Granham Smith J, et al. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. J Am Acad Dermatol 1983; 9: 933-6

39. Tschen Em Jones T. A new treatment for acne vulgaris combining benzoyl peroxide with clindamycin. J Drugs Dermatol 2002; 1: 153-7

40. Leyden JJ, Berger RS, Dunlap FE, et al. Comparison of the efficacy and safety of a combination topical gel formulation of benzoyl peroxide and clindamycin with benzoyl peroxide, clindamycin and vehicle gel in the treatments of acne vulgaris. Am J Clin Dermatol 2001; 2: 33-9

41. Ellis CN, Leyden J, Katz HI, et al. Therapeutic studies with a new combination benzoyl peroxide/clindamycin topical gel in acne vulgaris. Cutis 2001; 67 (2 Suppl.): 13-20

42. Cunliffe WJ, Holland KT, Bojar R, et al. A randomized, double-blind comparison of a clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. Clin Ther 2002; 24: 1117-33

43. Parry MF, Rha CK. Pseudomembranous colitis caused by topical clindamycin phosphate. Arch Dermatol 1986; 122: 583-4

44. Fisher AA. Adverse reactions topical clindamycin, erythromycin and tetracyclin. Cutis 1983; 32: 415-9

45. Krowchuk DP. Treating acne: a practical guide. Med Clin North Am 2000; 84: 811-28

46. White GM. Acne therapy. Adv Dermatol 1999; 14: 29-57

47. Mills Jr O, Thornsberry C, Cardin CW, et al. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. Acta Derm Venereol 2002; 82: 260-5

48. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003; 148: 467-78

49. Ross JI, Snelling AM, Eady EA, et al. Phenotypic and genotypic characterization of antibiotic-resistant *Propionibacterium acne*s isolated from acne patients attending dermatology clinics in Europe, the USA, Japan and Australia. Br J Dermatol 2001; 144: 339-46

50. Leyden JJ, McGinley KJ, Cavalieri S, et al. *Propionibacterium acnes* resistance to antibiotics in acne patients. J Am Acad Dermatol 1983; 8: 41-5

51. Eady EA, Cove JH, Holland KT, et al. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. Br J Dermatol 1989; 121: 51-7

52. Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. J Eur Acad Dermatol Venereol 2001; 15 Suppl. 3: 51-5

53. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant strain acne lesions from Europe. Br J Dermatol 2003; 148: 467-78

54. Knutson DD, Swinyer LI, Smoot WH. Meclocycline sulfosalicylate: topical antibiotic agent for the treatment of acne vulgaris. Cutis 1981; 27: 203-10

55. Kurokawa I, Akamatsu H, Nishijima S, et al. Clinical and bacteriologic evaluation of OPC-7251 in patients with acne: a double-blind group comparison study versus cream base. J Am Acad Dermatol 1991; 25: 674-81

56. Vogt K, Hanhn H, Hermann J, et al. Antimicrobial evaluation of nadifloxacin (OPC-7251), a new topical quinolone, in acne vulgaris. Drugs 1995; 49 (2 Suppl.): 266-8

57. Graupe K, Cunliffe W, Gollnick H, et al. Efficacy and safety of topical acid azelaic (20% cream): an overview of results from European clinical trials and experimental reports. Cutis 1996; 57 (1 Suppl.): 13-9

Correspondence and offprints: Prof. *Brigitte Dreno*, Department of Dermatology, Hotel Dieu, Pl. A. Ricordeau, 44093 Nantes Cedex 1, France.
E-mail: brigitte.dreno@wanadoo.fr