A Review of the Anti-inflammatory Properties of Clindamycin in the Treatment of Acne Vulgaris

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This article reviews anti-inflammatory properties of clindamycin, which is often used topically for the management of acne vulgaris, usually in combination with other agents. The efficacy of clindamycin in acne treatment has been shown to be sustained for more than 3 decades. It is likely that anti-inflammatory effects play an important role in the therapeutic activity of topical clindamycin.

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This article reviews anti-inflammatory properties of clindamycin, which is commonly used topically for the management of acne vulgaris. Topical clindamycin is most often utilized in combination with other topical agents, such as benzoyl peroxide, and/or a retinoid. Anti-inflammatory properties reported in association with clindamycin, expressed at the cellular and molecular level, may correlate with positive therapeutic outcomes observed during acne treatment. This article serves as a compilation of data from multiple sources that allow the reader to develop an overall appreciation for the potential therapeutic relevance of anti-inflammatory properties associated with topical clindamycin when used to treat acne vulgaris. Given these observations, it is not surprising that the combination of clindamycin and a topical retinoid in the same topical acne treatment regimen or single vehicle formulation (ie, clindamycin phosphate 1.2%–tretinoin 0.025% gel) is known to be more therapeutically effective than either drug used alone.[1-3]

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What information is available on the pathogenesis of acne that may correlate with the clinical relevance of anti-inflammatory properties of therapeutic agents used to treat acne vulgaris?

The pathogenesis of acne is not completely understood. However, it generally is agreed that development of acne lesions occurs in relation to several factors, including hormones, primarily androgenic stimulation of the sebaceous follicle (pilosebaceous unit); excess sebum production; abnormal follicular keratinization; follicular proliferation of *Propionibacterium acnes*; stimulation of innate immune response by *P acnes*; induction and perpetuation of an inflammatory cascade by several proinflammatory enzymes, cytokines, and chemokines; and a secondary inflammatory response to follicular disruption when present.[1,4-8]

Proinflammatory agents involved in the acnegenic inflammatory cascade include enzymes such as lipase that are known to release cytotoxic free fatty acids from sebum, as well as protease, hyaluronidase, and neuramidase. These enzymes can damage the follicular wall leading to leakage of contents into the surrounding dermis, which further propagates inflammation.[9-15] Other proinflammatory agents that have been associated with

P acnes include heat shock proteins, porphyrin, and squalene peroxides.[6,13,16,17]

The pilosebaceous unit can be considered an immunocompetent organ.[18] As such, it is sensitive to changes and stimuli that signal the beginning of a localized inflammatory process. Although the earliest sequence of events leading to an inflamed acne lesion remains somewhat controversial, generally it is accepted that the first objective evidence of a subclinical acne lesion is the microcomedone.[8] At this early stage, it is now believed that an inflammatory cascade may simultaneously occur in many cases.[19,20] In some affected follicles but not others, progression to the development of visible comedones and/or inflammatory acne lesions occurs.[8]

Importantly, *P acnes* releases potent low-molecular-weight (LMW) chemotactic factors and lipase enzyme during the early stages of preinflammatory and inflammatory acne lesion development.[21-26] These proinflammatory factors enter the dermis surrounding the follicle, thus attracting inflammatory cells such as neutrophils, monocytes/macrophages, and lymphocytes to the affected perifollicular region.[4,14,21,27-30]

Cytokines are LMW peptides and glycoproteins that represent components of the host response providing chemical communications and transmissions between cellular constituents of the immune system. Importantly, these chemical mediators serve to direct cellular "traffic" so that an organized immunologic defense can be mounted.[31] Within the extensive family of biologically active cytokines that *P acnes* can upregulate, 3 important subgroups play an important role as proinflammatory mediators during the early stages of acne lesion development: (1) chemokines, which function as chemotactic cytokines; (2) cytokines, which serve as messenger molecules; and (3) interleukins, which can serve to attract specific inflammatory cells.[31,32] Table 1 summarizes the spectrum of proinflammatory agents and subsequent inflammatory challenges associated with *P acnes*.

In acne lesion development, a variety of immunologically active cell types respond and contribute to the localized inflammatory cascade, including T cells, $CD4^+$ cells, and $CD14^+$ cells.[18,44,47-50] Activated monocytes transform into macrophages and begin to surround and engulf foreign materials present in the perifollicular region. Intracellularly, phagocytosing neutrophils and macrophages release various degradative lysosomal enzymes and toxic chemicals such as reactive oxygen species (ROS) that attempt to remove *P acnes* and its extracellular products.[51-54] With continued stimulation, the inflammatory cascade amplifies, the cycle perpetuates, and there is further damage and rupture of follicular wall integrity.[6,55-58]

Some other proinflammatory factors have been implicated as potential pathogenic mechanisms in acne vulgaris such as granulocyte-macrophage colony-stimulating factor (GM-CSF), leukotriene B_4, and HLA-DR.[7,14,18,47,59,60] Granulocyte-macrophage colony-stimulating factor promotes

Table 1.

Proinflammatory Agents Associated With Acne Lesion Development/ *Propionibacterium acnes*

P acnes Tissue Damage Factors	*P acnes* Chemotactic Factors	*P acnes* Cytokine Stimulant Factors	Proinflammatory Cytokine Early Response Factors (Chemokines/Interleukins/ Interferons/Others)
Fatty acids[6,15,33,34]	Lipase enzyme[23,37]	Heat shock proteins[13,16-18]	IL-1α[17,18,38-43]
Porphyrin[13,35,36]	Other neutrophil and immunocyte chemotactic factors[4,14,21,24,27-30]		IL-1β[41,44]
Squalene peroxides[6]			IL-6[17,38,39,42,43]
Protease, hyaluronidase, neuramidase[9,11,12,14,37]	C5a[18]		IL-8[41,44,45]
Keratin[1,6]			TNF-α[17,18,41,42]
			IFN-γ[18,46]

Abbreviations: TNF-α, tumor necrosis factor α; IFN-γ, interferon-γ.

growth of leukocytes involved in the inflammatory response, and leukotriene B_4 has been shown to recruit and activate neutrophils, monocytes, and eosinophils to sites of infection. This latter cytokine is synthesized from arachidonic acid through the combined action of the 2 enzymes 5-lipoxygenase and leukotriene A_4 hydrolase.[7,14,18,59,60] HLA-DR is a specialized protein upregulated by Langerhans cells during an infectious challenge, which helps to present antigens and activate the local immune response.[47] Complement-activated C5-derived neutrophil chemotactic factors attract more leukocytes and propagate further inflammation. Other important factors and mediators associated with *P acnes* inflammation are IL-12, toll-like receptors, activator protein-1 transcription factor, vascular cell adhesion molecules, degranulation in macrophages, growth factors, and expression of transglutaminase and lipoxygenase.[38,44,46,47,50,61-69]

What anti-inflammatory properties have been reported with clindamycin?

Clindamycin is a lincosamide antibiotic that exhibits an antibacterial mechanism of action by binding to the 50S ribosomal subunit of several microorganisms, including *P acnes*. When bound to this ribosomal site, it prevents the translocation of peptidyl–transfer RNA from the A site to the P site of the ribosome during protein synthesis.[26,70] As a result, the ribosome releases an incomplete protein, which adversely affects the viability of the organism. It also has been shown that clindamycin can interfere with the synthesis of the bacterial capsule that renders the bacterium more susceptible to phagocytosis.[71]

The anti-inflammatory properties of clindamycin that have been discussed in the literature are summarized in Table 2. The major indirect anti-inflammatory properties depicted in Table 2 are antibiotic activity, inhibition of protein synthesis, inhibition of lipase production, and reduction of fatty acid levels. The remaining anti-inflammatory properties described in Table 2 are referred to as direct anti-inflammatory actions of clindamycin.

What are the potential anti-inflammatory effects of clindamycin that may correlate with reduction of *P acnes*?

Follicular proliferation of *P acnes* generally is accepted as one of the major causative factors in acne pathogenesis.[1,4-7] By inhibiting the growth of *P acnes*, clindamycin reduces the presence of many chemotactic and cytotoxic proinflammatory agents produced by the organism. As such, the antibiotic effect of clindamycin serves to downregulate the inflammatory response because the source of these inflammatory mediators, namely *P acnes*, has been quantitatively suppressed. It has been established that clindamycin reduces the proliferation of *P acnes*.[72] As a result, the immunogenic potential of *P acnes* is diminished.

How does clindamycin-associated decrease in lipase production potentially correlate with anti-inflammatory activity in acne treatment?

Follicular proliferation of *P acnes* results in increased production of extracellular lipase, the enzyme responsible for the conversion of sebum triglycerides to free fatty acids.[23,37] Interestingly, subinhibitory levels of clindamycin against *P acnes* have been shown to suppress the in vitro production of lipase enzyme from 2 different strains of *Propionibacterium* species.[73] As a result, lower levels of free fatty acids have been observed in the sebum of patients with acne treated with clindamycin.[15,74]

Reduced levels of follicular free fatty acids, which are believed to be comedogenic and proinflammatory, have the potential to translate into a diminished inflammatory insult for the host. Reduced levels of free fatty acids reported in association with clindamycin represent an anti-inflammatory property of this compound.[15,73,74]

What effects have been observed with clindamycin on leukocyte chemotaxis?

Clindamycin has been shown to suppress leukocyte chemotaxis.[23,56,75,76] Because neutrophils are recognized as an important component of acne lesion development, this activity is felt to be a clinically relevant property of clindamycin in acne treatment. How does clindamycin exert an inhibitory effect on leukocyte chemotaxis? Extracellular lipase produced by *P acnes* has been shown to be chemotactic for neutrophils.[23,37,72] Furthermore, *P acnes* releases many LMW peptides that serve as potent chemotactic agents and are capable of attracting immunocytes to the infectious insult, especially neutrophils.[4,14,21-25,27-30] As a result, the ability of clindamycin to reduce *P acnes* organisms results in an indirect reduction of leukocyte chemotaxis. Additionally, clindamycin has been shown to markedly depress in vitro, C5-derived leukocyte chemotaxis, with minimal effect on random leukocyte migration.[75] This result was observed when clindamycin was used at concentrations less than, within, and greater than serum levels needed to

Table 2.

Anti-inflammatory Properties of Clindamycin

	Study Type		Inhibits		Enhances[a]	
Proinflammatory Factors and Components	**Acne[b]**	**Other**	**Yes**	**No**	**Yes**	**No**
Propionibacterium acnes growth	X[72]		X[72]			
P acnes protein synthesis (50S ribosomal subunit binding)		X[26,70]	X[26,70]			
P acnes lipase production	X[73]		X[73]			
P acnes and the release of follicular free fatty acids	X[15,74]		X[15,74]			
Proinflammatory Chemokines (Attractants)						
P acnes release of leukocyte chemotactic components	X[23,56,75,76]		X[23,56,75,76]			
IL-8	X[46,c]			X[46,c]		
Phagocytosis						
Opsonization of bacteria for enhanced phagocytosis		X[77-80]			X[77-80]	
Enhances and potentiates phagocytosis		X[77,81,82]			X[77,81,82]	
Respiratory burst (ROS as O_2^-, H_2O_2)		X[83,84]	X[83,84]			
iNOS enzymes		X[85]	X[85]			
Protein kinase C enzyme/granuloma formation	X[86]			X[86]		
Proinflammatory Cytokines (Primarily Monocytes)						
IL-1α	X[46,c]			X[46,c]		
IL-1β	X[46,d]	X[87-89]	X[46,87-89,d]			
IL-6	X[46,c,e]		X[46,c,e]			
IL-12p70	X[46,d]			X[46,d]		
IFN-γ	X[46,d]		X[46,d]			
TNF-α	X[46,d]	X[85,87-90]	X[85,87-90]	X[46,d]		
Keratinocyte Cytokines (Stimulants)						
GM-CSF	X[46,c,e]		X[46,c,e]			

Abbreviations: ROS, reactive oxygen species; O_2^-, superoxide; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor α; GM-CSF, granulocyte-macrophage colony-stimulating factor.

[a]In several instances, clindamycin can actually enhance rather than inhibit a process associated with inflammation. These enhancements can actually be beneficial therapeutically and therefore can be ranked as anti-inflammatory in nature.

[b]Acne related based on available understanding of inflammatory mechanisms involved in pathogenesis.

[c]From human keratinocytes activated by heat-killed *P acnes.*

[d]From human monocytes activated by heat-killed *P acnes.*

[e]Inhibits at high concentration; however, the investigators suggest that the high concentration of clindamycin used "may be achievable in acne lesions after single topical application . . ."[46]

exhibit antibiotic activity, which suggested a direct inhibitory effect on leukocyte chemotaxis. Furthermore, it also has been demonstrated that clindamycin can suppress leukocyte chemotaxis using *P acnes* in vitro models.[23,56,75,76]

What effects have been observed with clindamycin on phagocytosis and opsonization of bacteria?

When considered as an overall effect, enhanced phagocytosis may have anti-inflammatory value. Homeostatic levels of phagocytosis are considered to be an anti-inflammatory response because removal of unwanted bacteria, extracellular by-products, and other proinflammatory debris is beneficial to the host. However, if an amplified inflammatory cascade becomes chronic and excessive, continued phagocytosis can exacerbate inflammation.[51-54] It has been noted that macrophages can initially add to the inflammatory process; however, when activated to another bioactive form, they can actually aid in the healing process,[91] which would explain how many severely inflamed sites resolve favorably without outside intervention and leave behind functionally and histologically unaffected tissues.

Clindamycin has been shown to potentiate the activity of phagocytic leukocytes.[77] Reported phagocytic activities of clindamycin include marked enhancement of phagocytosis of 4 different strains of *Bacteroides* species, elevation of the percentage of phagocytosing polymorphonuclear leukocytes obtained from gingival crevice fluids, and cellular surface changes of *Staphylococcus aureus* that render it far more susceptible to phagocytic cells.[77,81,82] Presently it is not known if enhancement of phagocytosis by clindamycin is an operative mechanism related to the efficacy of this agent in acne treatment; however, this activity is a potential anti-inflammatory effect of clindamycin.

With regard to opsonization of bacteria, phagocytosis of *Bacteroides thetaiotaomicron* was enhanced in the presence of clindamycin.[77] At subinhibitory concentrations, clindamycin has been shown to enhance the uptake of *S aureus* by phagocytic cells, an effect believed to be due to enhanced opsonization.[78] Additionally, the phagocytosis of *S aureus* 502A, grown in the presence of one-third of the minimum inhibitory concentration of clindamycin, was substantially enhanced compared to the untreated control.[79] In the presence of subinhibitory concentrations of clindamycin, *Streptococcus pyogenes* organisms were denuded of cell surface M protein, thus rendering them more susceptible to phagocytosis by polymorphonuclear leukocytes.[80]

What effect does clindamycin have on macrophage respiratory burst?

When macrophages digest and degrade engulfed pathogenic organisms (eg, *P acnes*), intracellular release of cytotoxic ROS, such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), is known as respiratory or oxidative burst. Clindamycin is known to concentrate inside human phagocytic cells.[71,83,92,93] Once inside the cell, it can potentially modulate the stimulated output of superoxides through an inhibitory effect. In vitro stimulus-activated neutrophil systems have shown that clindamycin modestly suppressed superoxide production in a formyl-methionyl-phenylalanine–stimulated system, substantially inhibited superoxide production by approximately 50% when a microbial particle-stimulated model was used, and also suppressed the release of hydrogen peroxide.[83] Along the same lines, clindamycin caused dose-related inhibition of in vitro superoxide formation by both untreated and pyocyanin-treated neutrophils as well as inhibition of ROS using other neutrophil-stimulated models.[84]

What effect does clindamycin have on IL-1α and IL-1β?

Human keratinocytes, macrophages, and monocytes are a major source of IL-1α and IL-1β during the cutaneous immune response to *P acnes* proliferation, with IL-1α expressed in correlation with comedone formation in vitro in isolated pilosebaceous units.[39] Furthermore, in vivo assessments of IL-1α in comedones have shown that it can induce inflammation when released into the dermis.[40] Four in vitro studies have shown that clindamycin inhibits the production of proinflammatory IL-1β.[46,87-89] Inhibition of IL-1β production may be part of the mode of action of clindamycin in the treatment of acne vulgaris.[89] Clindamycin does not inhibit the production of IL-1α by human keratinocytes.[46]

It has been shown that *P acnes* and supernatants obtained after 72 hours of *P acnes* growth markedly increased the induction of proinflammatory IL-1β in human monocyte cell lines.[32,41] An in vitro study was conducted in which human peripheral blood mononuclear cells and healthy human epidermal keratinocytes were used to measure, in part, the inhibitory effect of clindamycin on proinflammatory cytokines, including IL-1β.[46] Heat-killed *P acnes* served as the stimulus for upregulating cytokine production in these human cell lines. The investigators showed that clindamycin remarkably inhibited the production of proinflammatory IL-1β by human monocytes.[46]

Investigators also have demonstrated that clindamycin modulates cytokine production after exposure of mouse peritoneal macrophages to lipopolysaccharide (LPS) antigen, which is known to activate macrophages.[87] Specifically, clindamycin "decreased the intracellular expression levels of . . . interleukin 1β (IL-1β) and increased IL-6 expression in macrophages . . . . Our findings suggest that [clindamycin] modulates cytokine production in LPS-stimulated macrophages."[87] In 2 other studies, clindamycin inhibited the in vivo production of IL-1β in mice subjected to *Escherichia coli*–induced toxic shock endotoxin, and human acute monocytic leukemia cell line cells produced less IL-1β when exposed to *E coli* previously treated with this drug to suppress endotoxin formation.[88,89]

What effects have been reported with clindamycin on production of interferon-γ?

Results showed that clindamycin inhibited the production of interferon-γ (IFN-γ) by human monocytes, which may have an effect in reducing inflammation.[46] Interferon-γ primes macrophages so that they produce degradative lysosomal activity, plays a key role in antigen processing of macrophages, and induces the production of E selectin on endothelial cells as well as intercellular adhesion molecule-1 and HLA-DR on keratinocytes; all of these processes play an important role in the attraction of leukocytes to the site of infection. Also, the generation of T cell lines from inflamed acne lesions and cytokine response after exposure to *P acnes* antigens have been explored. The results showed that the antigens were recognized and that several proinflammatory mediators were upregulated, most notably IFN-γ. The authors suggested that "IFN-γ may play a central part in the immunopathogenesis of acne."[94] Heat-killed *P acnes* served as the stimulus for upregulating cytokine production in human peripheral blood mononuclear cells, with clindamycin shown to substantially inhibit the production of IFN-γ by human monocytes.[46]

What effects have been reported with clindamycin on production of tumor necrosis factor α?

Tumor necrosis factor α (TNF-α) is a multifunctional cytokine that plays an important role in immunologic response, including upregulation of many prostaglandins, collagenase enzymes, and various inflammatory cells, as well as release of several cytokines, such as IL-1, IL-6, IL-8, and GM-CSF.[41,42,46] One of the earliest expressions of the inflammatory response is the activation of cellular adhesion molecules that serve to traffic inflammatory cells into peripheral tissues, a response that appears to be under the control of TNF-α and IL-8. Tumor necrosis factor α can be produced by human keratinocytes when stimulated with UV light or LPS endotoxins that activate macrophages.[42] Overall, TNF-α can upregulate and induce a broad range of secondary proinflammatory effects in response to pathogenic organisms, including *P acnes*.

Multiple studies that employed various in vitro models demonstrated that clindamycin can inhibit the production of TNF-α, including LPS-induced macrophages. This inhibitory effect could potentially translate into therapeutic anti-inflammatory activity at the clinical level.[85,87-90] One study reported that clindamycin did not inhibit the production of TNF-α when *P acnes* was used to stimulate human peripheral monocytes.[46]

What effect does clindamycin have on nitric oxide synthase enzymes and nitric oxide formation?

Nitric oxide (NO) is synthesized from arginine and oxygen by various inducible nitric oxide synthase (iNOS) enzymes. Nitric oxide is an important cellular mediator of inflammatory and vascular responses in various organ systems, including skin. Some proinflammatory cytokines can induce excessive quantities of NO via induction of iNOS, ultimately stimulating inflammatory responses that can lead to cellular damage.[93] In one study, clindamycin was shown to decrease the ability of group B streptococci to stimulate iNOS accumulation in macrophages, an effect that results in decreased production of NO.[85]

What effects have been reported with clindamycin on production of IL-6?

IL-6 is an immune cytokine with a wide range of proinflammatory and anti-inflammatory properties. In the presence of IL-1, IL-6 is secreted by macrophages, T lymphocytes, and keratinocytes, with decreased IL-6 production resulting in a marked decline in the acute inflammatory response. IL-6, a proinflammatory mediator in inflammatory acne, has been shown to be secreted by peritoneal macrophages using an in vitro *P acnes*–induced cytokine production model.[44]

Healthy human keratinocyte cells were used in an in vitro study to evaluate the inhibitory effect of clindamycin on IL-6 induction when heat-killed *P acnes* served as the stimulus for upregulation.[46] The study showed that use of clindamycin at the highest concentration (ie, 30 μg/mL) inhibited the production of IL-6 by human keratinocytes. The authors also pointed out that the inhibitory tissue concentration is achievable after topical application of clindamycin.[46]

What effects have been reported with clindamycin on production of GM-CSF?

Granulocyte-macrophage colony-stimulating factor is a proinflammatory proteinaceous cytokine secreted by macrophages, other immune cells, and keratinocytes. It is a component of the inflammatory cascade that can stimulate production of large numbers of macrophages in response to an inflammatory challenge.[46]

The same in vitro study described earlier for IL-6 also was employed to evaluate the inhibitory effect of clindamycin on GM-CSF production by human keratinocytes. Heat-killed *P acnes* served as the stimulus for upregulating the GM-CSF cytokine. Once again, the investigators demonstrated that clindamycin decreased production of GM-CSF by healthy human keratinocytes.[46]

What other effects or lack of effects have been reported with clindamycin that relate to anti-inflammatory properties?

Clindamycin did not inhibit induction of IL-1α and IL-8 in human keratinocytes when heat-killed *P acnes* was used as the activating agent nor did it inhibit the production of IL-12p70 in human monocytes activated by heat-killed *P acnes*.[46] It also has been observed that clindamycin does not have an inhibitory effect on the activity of protein kinase C, an agent whose presence has been linked to more severe forms of acne.[86]

What conclusions can be drawn on anti-inflammatory effects of clindamycin from the information described?

A myriad of articles have been published, as referenced here, discussing several immunomodulatory properties of clindamycin. Many of these anti-inflammatory effects may correlate with therapeutic activity in acne vulgaris, especially those effects related to inhibition of cytokines that promote the innate inflammatory response.[39,40,46,87-89] It should be noted that anti-inflammatory properties of clindamycin often are referred to as indirect and direct. The term *indirect* should not be confused with lesser activity. It is not entirely clear which anti-inflammatory properties play major or minor roles in acne treatment; however, the net effect of these anti-inflammatory properties suggest that the efficacy of clindamycin in acne treatment is not likely related to antibacterial activity alone. As the efficacy of clindamycin in acne treatment has been shown to be sustained for more than 3 decades, despite the emergence of clindamycin-resistant *P acnes* strains in some patients, it is likely that anti-inflammatory effects play an important role in the therapeutic activity of topical clindamycin.[95]

The clinical ramifications suggested by these in vitro observations are supported by the results of many clinical studies that demonstrate the efficacy of topical clindamycin in acne treatment.[95] It also has been shown that topical clindamycin alone or in combination with topical tretinoin is able to reduce both inflammatory and noninflammatory acne lesions.[2,95-98] Importantly, it is not suggested that topical clindamycin be used as monotherapy for the treatment of acne; however, monotherapy studies do substantiate its therapeutic value in acne treatment.[1,95-99]

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