Docket No.: 512-53

METHODS OF TREATING ACNE

Inventor: Robert A. Ashley

Hoffmann & Baron, L.L.P.
6900 Jericho Turnpike
Syosset, New York 11791
(516) 822-3550

METHODS OF TREATING ACNE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/281,916, filed April 5, 2001, and U.S. Provisional Application No. 60/325,489, filed September 26, 2001, both of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Acne is a common disease characterized by various types of lesions. The areas affected typically are areas of the skin where sebaceous glands are largest, most numerous, and most active. The lesions associated with acne are usually categorized as either non-inflammatory or inflammatory.

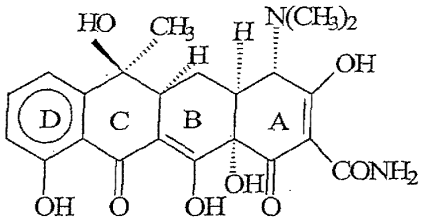
Non-inflammatory lesions include comedones. Comedones appear in two forms, open and closed. Comedones are thought to arise from abnormal follicular differentiation. Instead of undergoing shedding and discharge through the follicular orifice, abnormal desquamated cells (keratinocytes) become unusually cohesive, forming a microcomedo or a microscopic hyperkeratotic plug in the follicular canal. The progressive accumulation of these microcomedones lead to visible comedones.

In its mildest form, acne is a more or less superficial disorder characterized by slight, spotty skin irritations. In such cases, ordinary skin hygiene is typically a satisfactory treatment. In the more inflammatory types of acne, however, pustules; infected cysts; and in extreme cases, canalizing, inflamed and infected sacs appear. Without effective treatment, these lesions may become extensive and leave permanent, disfiguring scars.

Microorganisms, especially *Propionibacterium acnes*, are strongly implicated in the pathogenesis of acne. The microorganisms are thought to release microbial mediators of inflammation into the dermis or trigger the release of cytokines from ductal keratinocytes.

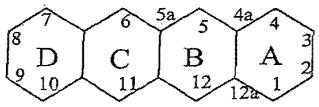
Accordingly, the efficacy of antibiotics in treating acne is thought to be due, in significant part, to the direct inhibitory effect of the antibiotics on the growth and metabolism of these microorganisms. Systemically-administered tetracycline antibiotics, especially minocycline hydrochloride, are particularly effective in treating acne.

The tetracyclines are a class of compounds of which tetracycline is the parent compound. Tetracycline has the following general structure:



Structure A

The numbering system of the multiple ring nucleus is as follows:



Structure B

Tetracycline, as well as the 5-hydroxy (oxytetracycline, e.g. Terramycin) and 7-chloro (chlorotetracycline, e.g. Aureomycin) derivatives, exist in nature, and are all well known antibiotics. Semisynthetic derivatives such as 7-dimethylaminotetracycline (minocycline) and 6α-deoxy-5-hydroxytetracycline (doxycycline) are also known tetracycline antibiotics. Natural tetracyclines may be modified without losing their antibiotic properties, although certain elements of the structure must be retained to do so.

In addition to the direct antibiotic activity of tetracyclines, further activities of antibiotic tetracyclines have been investigated for possible therapeutic effects on acne.

For example, a study by Elewski et al., *J. Amer. Acad. Dermatol.*, *8*:807-812 (1983) suggests that acne therapy, consisting of orally-administered tetracycline at a total daily dose of 1000 mg, may have therapeutic anti-inflammatory effects in addition to antibiotic effects. In particular, it was found that the anti-inflammatory effect of tetracycline was, at least in part, due to inhibition of neutrophil chemotaxis induced by bacterial chemotactic factors.

A more recent study, performed by Eady et al., *J. Invest. Dermatol.*, *101*:86-91 (1993), evaluated the effects of oral minocycline or tetracycline therapy on the cytokine and microflora content of open comedones in acne patients. The total daily dose of minocycline administered was 100 mg. The total daily dose of tetracycline administered was 1000 mg.

Eady et al. found that the therapies upregulated the production of bioactive IL-1α-like material and immunochemical IL-1β. IL-1 is considered to be a pro-inflammatory cytokine.

Accordingly to Eady et al., no overall decrease in the numbers of propionibacteria/mg of comedonal material was found. It is important to note, however, that the numbers of propionibacteria/mg of comedonal material are not expected to decrease in response to antibiotic therapy. Since the bacteria within comedones are encapsulated by the follicle, they are not susceptible to antibiotic treatment.

Another possible activity of tetracyclines in acne therapy was investigated by Bodokh, I., et al., *Acta. Derm. Venerol.*, *77*:255-259 (1997). Their study was designed to evaluate the action of minocycline on sebaceous excretion in acne patients. A 100 mg daily dose of minocycline was administered. A subclinical increase in seborrhoea was reported. The authors propose that minocycline induces an increase in seborrhoea via a reduction in ductal obstruction. The mechanism by which the ductal obstruction is reduced is proposed to be a reduction in ductal

irritation. The authors suggest that the reduction of ductal irritation is due to minocycline's direct effect on *P. acnes*, or minocycline's effect on the lipase produced by *P. acnes*.

Bodokh et al. also found that during treatment no correlation exists between seborrhoea intensity and clinical severity of acne. The authors state that the lack of correlation shows that seborrhoea is pathogenic because it is the "culture medium" of *P. acnes*. Thus, it can be concluded that the authors consider the antibiotic activity of minocycline to be therapeutically significant with respect to acne.

Similarly, in a recent clinical study it was reported that tetracycline in sub-antibiotic doses had no clinical effect on acne. (Cunliffe et al., *J. Am. Acad. Dermatol.*, *16*:591-9 (1987).) In particular, a 100 mg total daily dose of minocycline and a 1.0g total daily dose of tetracycline were found to be necessary to successfully treat acne.

The antibiotic effects of antibiotics are generally directly proportional to the dose administered of the antibiotics. Accordingly, in moderate to severe (i.e. inflammatory) forms of acne, oral antibiotics are typically administered at high doses. For example, in conventional acne therapy, tetracycline is administered at an initial dose of 500 to 2,000 mg/day, followed by a maintenance dose of 250-500 mg/day.

Clearly, the state-of-the-art teaching is that the clinical efficacy of systemically-administered tetracyclines in the treatment of acne is due, at least in significant part, to the antibiotic effects of the tetracyclines. In addition to their antibiotic effects, it has been proposed that tetracyclines reduce the number of inflammatory lesions (papules, pustules and nodules) by a variety of non-antibiotic mechanisms. Such mechanisms include interfering with the chemotaxis of polymorphonuclear leukocytes (PMN) into the inflammatory lesion, inhibition of PMN derived collagenase, and by scavenging reactive oxidative species produced by resident inflammatory cells.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.