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A New Tetracycline for Acne: The Role of Sarecycline

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ABSTRACT

INTRODUCTION AND OBJECTIVE

A common dermatological disorder that significantly affects both the physical appearance and mental well-being of patients is acne vulgaris. Its presence is frequently associated with reduced quality of life due to its chronic nature, visible lesions, and the risk of permanent scarring. The pathogenesis of acne is multifactorial and includes follicular hyperkeratinization, colonization of the skin by *Cutibacterium acnes*, inflammation, and overproduction of sebum. The purpose of this article is to present sarecycline, a third-generation tetracycline antibiotic approved by the United States Food and Drug Administration in 2018 for the treatment of

moderate to severe acne vulgaris. The review summarizes current scientific findings regarding its clinical efficacy and safety profile.

MATERIALS AND METHODS

This article is based on a literature review concerning the therapeutic application of sarecycline in acne vulgaris. A comprehensive search was conducted using scientific databases including PubMed and Google Scholar, covering the period from 1999 to 2024. Keywords such as acne, tetracycline, and sarecycline were used to identify relevant studies.

CONCLUSION

Compared to traditional tetracyclines, sarecycline demonstrates limited activity against Gram-negative bacteria, which helps reduce the incidence of gastrointestinal side effects. Due to its favorable efficacy and safety profile, it is considered a valuable treatment option, especially for patients requiring long-term antibiotic therapy. Sarecycline has the potential to redefine established treatment paradigms in the management of acne vulgaris.

KEYWORDS: sarecycline, tetracycline, acne vulgaris

1. INTRODUCTION

Acne vulgaris is among the most common skin diseases, occurring in men and women of all ages but mostly in adolescents and young adults. Epidemiological studies show that facial acne affects around 54% of adult females and 40% of adult males, with manifestations for some extending well beyond adolescence [1]. Although, It is frequently considered a self-limiting disease, acne is an immediate and long-term psychosocial burden. This phenomenon leads to patients loss of self-confidence, social anxiety, and clinical symptoms of depressive disorder, which severely reduce patients' quality of life [2, 3]. The microcomedone (subclinical blockage of the follicular infundibulum) is the first lesion in acne pathogenesis. As the disease progresses, microcomedones may develop into inflammatory papules, pustular lesions, nodules, or cystic formations, with some cases ultimately resulting in permanent scarring in

patients [4]. Multiple endogenous and environmental factors are recognized as participating in the acne course [4]. Hormonal fluctuations, especially high levels of androgens, as well as consumption of high-glycemic-load diets and dairy products have also been associated with sebaceous hyperactivity and inflammation [6, 4, 5, 7]. Moreover, lifestyle and environmental exposure (smoking, psychological stress, ultrasound radiation and airborne polluted particles) can also aggravate acne severity and inflammation [6,8, 9,10, 11]. Other important

considerations include a number of pharmacological agents that can exacerbate acne or be responsible for its induction. Exogenous androgens, anabolic steroids, glucocorticoids, antiepileptic drugs, some psychotropic medications, and high-dose vitamin B12 supplementation may all lead to the development of these cysts [6]. The mechanisms are heterogeneous but generally include increased sebaceous gland activity, modified keratinocyte proliferation, immune modulation, and skin microbiota disruption. Among these, anabolic-androgenic steroids, which are especially used in non-medical context such as bodybuilding, serve as potent triggers. These agents contribute to the sensitivity of sebaceous glands to androgens by upregulating androgen receptors in the pilosebaceous unit, stimulating sebum production, follicular occlusion, and inflammatory lesion formation [7]. Acne reflects an imbalance between innate and adaptive immunity, involving a complex interplay of cellular and humoral components. Key elements of the immune response include CD3+ and CD4+ T lymphocytes, interleukin-1 (IL-1), integrins, Toll-like receptors (TLRs), and macrophages. At the heart of the inflammatory cascade is Cutibacterium acnes, a Gram-positive, anaerobic commensal bacterium that occupies pilosebaceous follicles. During dysregulation, the expansion of Cutibacterium acnes and interactions with host innate immunity contributes to the maintenance of cutaneous inflammation [12, 13]. Tetracyclines, which show antibacterial and anti-inflammatory properties, are often used in cases of acne with a predominantly inflammatory component. Conventional tetracyclines, for example, doxycycline and minocycline, are wide-spectrum agents successful against Gram-negative microbes just as Cutibacterium acnes. Sarecycline is a third-generation, narrow-spectrum tetracycline antibiotic that was approved by the U.S. Food and Drug Administration (FDA) in 2018 for the treatment of patients with moderate to severe acne as an oral therapy. Because of its selective mechanism of action, sarecycline has lower impact on gut microflora and a better safety profile than classical tetracyclines [14].

2. MATERIALS AND METHODS

In this narrative review we aimed to provide a summary of the available knowledge on the pharmacological properties, clinical efficacy, and safety of sarecycline for patients with acne vulgaris Searching strategy included an analysis of the materials collected in PubMed and Google Scholar databases using the following terms: sarecycline, tetracycline, acne vulgaris, narrow-spectrum antibiotic, Cutibacterium acnes, antibiotic resistance and gut microbiota. All relevant peer-reviewed articles from October 1999 until February 2024 in English were included. Studies were selected according to their relevance to the mechanism of action, pharmacokinetics, antimicrobial activity, clinical indications for acne management,

and safety outcomes of sarecycline. Ultimately, 37 articles met the inclusion criteria and were reviewed.

3. PHARMACOLOGY

Tetracyclines act by causing inhibition of protein synthesis through reversible binding to the A site of 30S ribosomal subunit. This interaction blocks the incorporation of aminoacyl-tRNA into the elongating polypeptide chain, thereby stopping translation and blocking bacterial reproduction [13, 17]. Sarecycline, a third-generation oral tetracycline, retains this core mechanism, but features structural alterations that provide enhanced pharmacological specificity. The most unique aspect of sarecycline's chemical structure is the substitution at position C7 on the D ring: a large 7-[[methoxy(methyl)amino] methyl] branched chain that is unprecedented among tetracycline agents. This extended moiety enables further molecular interactions in the ribosomal tunnel, beyond the classical binding site, which could add stability to the drug–ribosome complex and enhance its antibacterial effect—especially against Cutibacterium acnes [13,15,16]. Sarecycline pharmacokinetically exhibits a favorable profile for long-term therapeutic exposure. Peak concentrations in plasma after oral administration of sarecycyline is generally achieved in 1.5 and 2 h. The drug has a long elimination half-life of about 21 to 22 hours, allowing once-daily administration. It has moderate plasma protein binding (62%-75%) and large volume of distribution, indicative of extensive tissue penetration. Hepatic metabolism is minimal, with renal and fecal routes accounting for most of the excretion, largely in unchanged form [27, 26].

4. TREATMENT

4.1 ADMINISTRATION OF SARECYCLINE

First- and second-generation tetracyclines are capable of chelating metal ions (Fe, Ca, Mg, and Al), resulting in poorly soluble complexes that greatly diminish their bioavailability. Consequently, the simultaneous administration of tetracyclines with milk, iron supplements, or other metal ion-rich products can reduce absorption by 50–90% [5]. Moreover, addition of foods high in fat and carbohydrate with these antibiotics may considerably decrease their serum concentrations [18,22]. Sarecycline is a novel third-generation tetracycline antibiotic with unique pharmacokinetic properties. Its absorption is less influenced by the presence of food compared to traditional tetracyclines, so it can be given on an empty stomach or with meals. Sarecycline should be taken once daily with a full glass of water to reduce the risk of esophageal irritation and ulceration [18,20]. The recommended doasge of sarecycline for patients aged 9 years or older depends on body weight: 60 mg for patients weighing 33–54 kg,

100 mg for patients weighing 55–84 kg, and 150 mg for patients weighing 85–136 kg [19]. Like other tetracyclines, sarecycline is contraindicated during pregnancy and is classified as a Category D agent by the FDA. This classification indicates the likelihood of adverse fetal consequences, especially if the agent is encountered during active organogenesis. Tetracyclines as a drug class have been associated with permanent tooth discoloration and enamel hypoplasia when individuals are exposed in utero, along with inhibition of fetal bone development via calcium binding in the developing tissues. Maternal side effects are rare but serious the most concerning being hepatotoxicity and gastrointestinal injury [21, 22, 23]. Although data directly related to sarecycline are limited, it is chemically similar to other tetracyclines with similar risk during pregnancy. Importantly, the major teratogenic window seems to be in the first trimester, when skeletal and dental tissues develop [21, 22, 29]. Retrospective data regarding other tetracyclines, like doxycycline, indicate short-term use is unlikely to substantively elevate overall risk for malformations. Due to a lack of large, controlled studies in pregnant populations, the teratogenic potential of sarecycline cannot be definitively assessed [21, 22, 23]. Hence, sarecycline should be avoided during pregnancy unless unequivocally warranted when no safer alternative is available. Potential maternal benefits need to be balanced against potential fetal risks, especially in early gestation [21,22,23].

4.2 SPECTRUM OF ACTIVITY OF SARECYCLINE

Sarecycline is a third-generation tetracycline-class antibiotic with a reduced spectrum of activity and selective activity against Gram-positive organisms including Cutibacterium acnes, the principal bacterium implicated in the pathogenesis of acne vulgaris. It is also effective in other Gram-positive bacteria, including Staphylococcus aureus, and its antimicrobial potency is similar to that of old tetracyclines such as doxycycline, minocycline, and tetracycline [12, 24, 25]. Unlike the broad-spectrum tetracyclines, sarecycline has limited activity against Gram-negative enteric pathogens, such as Proteus mirabilis, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, and Salmonella spp. [24]. This more restricted range of activity has clinically relevant implications for microbiome preservation. Both clinical and microbiological studies suggest that sarecycline produces only modest and transient changes to the gut microbiota. Small reductions in abundance of bacteria like Ruminococcaceae and Desulfovibrionaceae have been observed during treatment, with rapid recovery after finishing the therapy [24, 25]. As sarecycline has a microbiota-sparing profile when compared to doxycycline and minocycline, which are known to decrease gut microbial diversity and allow

opportunistic species such as Enterobacteriaceae to overgrow, it may lower the risk of antibiotic-associated complications and allow for an approach toward longer-term use [24, 25, 34].

4.3 RESULTS

Two well-designed phase III randomized, double-blind, placebo-controlled clinical trials, which included a total of 2,002 patients aged 9 years and older, have shown sarecycline for treating moderate to severe acne vulgaris. Sarecycline was administered orally as a 1.5 mg/kg daily dose for 12 weeks [12, 28]. Treatment outcomes were evaluated using the Investigator's Global Assessment (IGA) scale that reflects acne severity on a spectrum from 0 (clear skin) to 4 (severe acne). A clinical response was determined as a decrease of 2 or more points on the IGA scale and reaching a final score of "clear" or "almost clear [12, 14, 19, 27, 35]. At the end of the 12-week treatment period, 21.9%–22.6% of sarecycline-treated patients achieved this defined therapeutic success versus 10.5%–15.3% in the placebo group ($p < 0.0001$). There was also a significant reduction in inflammatory lesion counts with reductions from 49.9%–51.8% in the sarecycline group compared to 35.1%–35.4% in the placebo group ($p < 0.0001$) [14, 27]. Furthermore, sarecycline helped reduce non-inflammatory lesions like comedones. Average lesion number decreased by 15.1–16.2 in the treatment group and 11.2–13.4 in placebo ($p < 0.01$) [27]. Significantly, those findings did not only pertain to facial involvement: in truncal acne (involving the chest and back), 29.6% to 36.6% of patients treated with sarecycline experienced at least a two-point improvement on the Investigator's Global Assessment (IGA) scale, compared with 19.6% to 25.7% in the placebo group ($p < 0.05$) [19]. A subgroup analysis of the Hispanic subset of participants ($n = 550$) reported a rapid therapeutic response, with a 26% reduction in inflammatory lesions at week 3 ($p = 0.0279$). Further improvement was observed over the course of treatment with lesion volume size reductions of 41% at week 6 ($p = 0.0003$) and 55% at week 12 ($p < 0.0001$). These differences are likely due to ethnic background and related discrepancies in the human microbiome profiles that might affect treatment response [36]. In summary, sarecycline demonstrated consistent activity in reducing inflammatory and non-inflammatory acne lesions across different anatomical sites. The early onset of action in specific populations, along with its efficacy in truncal acne, suggest that sarecycline might play a role outside its conventional site of action [14, 35].

4.4 SIDE EFFECTS

Tetracyclines, despite being well tolerated in most patients and safe for the treatment of a variety of bacterial infections and dermatologic disorders, are routinely associated with some

side effects. The reported side effects most frequently associated with polyphenols are gastrointestinal disturbances related to their influence on the intestinal microbiota, such as nausea, vomiting, diarrhea, and abdominal pain [30]. Chronic use can alter gut flora balance, and becomes a risk factor for pathogenic colonization, with immunological outcomes [29]. Photosensitivity (phototoxicity) is another important adverse effect (especially with doxycycline), presenting as sunburn-like responses after limited exposure to UV radiation [31, 37]. Moreover, hematologic disorders (eg, eosinophilia, thrombocytopenia, and hemolytic anemia) have been reported with tetracyclines, albeit less frequently [29]. It can also cause immunological reactions in susceptible individuals, such as drug-induced lupus-like syndrome, autoimmune hepatitis, and hypersensitivity syndrome with fever, rash, and dysfunction of internal organs [30]. Tetracyclines are also known to accumulate in calcium-rich tissues, particularly in bone and teeth, leading to permanent tooth discoloration and inhibition of bone growth in children younger than 8 years [29]. Tetracyclines do have some notable, albeit uncommon, complications including pseudomembranous colitis, intracranial hypertension, and ototoxicity manifesting as tinnitus and hearing disturbances [30]. This wide variety of potential side effects means that tetracycline use should be cautious in patients with autoimmune diseases, hematologic abnormalities, and gastrointestinal diseases [29, 30, 31]. The generation of new tetracyclines, including sarecycline, has reduced the antibacterial spectrum leading to decreased possible adverse effects. However, their long-term safety profile remains an area of active investigation [12]. In comparsion to other tetracyclines, sarecycline is characterized by an improved safety profile, which can be ascribed to both the reduced antibacterial spectrum and its low penetration of the blood–brain barrier [33]. Minocycline is the most lipophilic tetracycline and penetrates well into the central nervous system, which is associated with a higher incidence of vestibular adverse effects including dizziness, nausea, and imbalance [26]. Review of animal model studies has demonstrated that sarecycline has considerably less chance of penetrating the blood–brain barrier; this mechanism may contribute to the lower frequency of neurological adverse effects recorded among those receiving this agent [26, 33,32]. Sarecycline, like other tetracyclines, can cause photosensitivity reactions, however, the incidence is lower than broad-spectrum antibiotics such as doxycycline [26, 33, 37]. The overall incidence was low [26, 12], and there have been only isolated reports of sunburn and phototoxic reactions in clinical trials. In terms of gastrointestinal adverse effects, the most frequently reported gastrointestinal symptom in humans treated with sarecycline is nausea [34, 24]. However, its incidence is only slightly greater than that seen in the placebo group. Moreover, the risk of vomiting, diarrhea,

or esophagitis is lower than in other tetracyclines [33]. In addition, while antibiotics in this group are associated with increased risk of vaginal candidiasis in women, the rates of this complication in sarecycline-treated patients were comparable to or decreased compared with those seen in broad-spectrum tetracyclines [26]. Sarecycline is more selective in its antibacterial activity and is less likely to interfere with gut microbiota—factors that are likely to limit overall risk of gut microbiome-related dysbiosis (i.e. imbalance of gut microbiota) and associated complications such as opportunistic infections or gastrointestinal symptoms [27, 33, 34]. Sarecycline, therefore, provides a safer treatment option than other tetracyclines, especially for patients who require prolonged use of antibiotics (e.g., acne vulgaris) [12, 26, 27, 33, 34].

5. SUMMARY

Sarecycline is a third-generation, narrow-spectrum tetracycline, it is reflecting a growing trend towards targeted antimicrobial strategies to minimize the extraneous damage wrought by broad -spectrum agents. This narrowed mechanism of action, primarily directed towards Gram-positive bacteria, particularly Cutibacterium acnes, offers a considerable therapeutic benefit in acne vulgaris, especially in the presence of chronic antibiotic therapy. Unlike older tetracyclines, sarecycline has weak activity against commensal Gram-negative bacteria, making it less likely to cause gastrointestinal disturbances, including dysbiosis, nausea, or antibiotic-associated diarrhea. That growing line of defence, along with its stable pharmacokinetics and food-independent absorption characteristics, renders a level of treatment convenience and tolerability that optimally promotes long-term adherence and provides a degree of patient satisfaction. Multiple clinical trials have shown sarecycline's ability to reduce both inflammatory and non-inflammatory acne lesions with a lower incidence of adverse effects than traditional therapies. These findings imply that sarecycline may act as a first-line agent in moderate-to-severe acne, but also as a safer long-term therapeutic option in patients susceptible to treatment-related adverse events or with comorbid gastrointestinal sensitivity. However, long-term studies, including studies on ethnically diverse population, are needed to confirm the long-term continued efficacy and safety of the drug in a broader range of clinical situations. Although sarecycline is only approved in the United States to date, its therapeutic profile lends itself well for incorporation into international acne management guidelines and clinical practice pathways.

Disclosure

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