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The Use of Metronidazole and Doxycycline in Dermatological Infections: A Systematic Review

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Abstract
This comprehensive review examines the use of metronidazole and doxycycline in treating dermatological infections, outlining their mechanisms of action, indications, dosages, side effects, as well as potential drug interactions. Additionally, this review compares the efficacy, tolerability, safety and cost-effectiveness of these two antibiotics as well as explores the rationale and evidence supporting combination therapy. In light of the growing concern of antibiotic resistance in dermatology, this article addresses strategies to minimize resistance development and emphasizes patient education and compliance. Adjudicious use of metronidazole and doxycycline, along with an understanding of their properties and roles within dermatology, are critical elements in providing safe yet effective treatments for those suffering from skin infections.

Keywords-Metronidazole, Doxycycline, ACNE, Dermatological Infections

I. Introduction

Dermatological infections, including bacterial, fungal and viral ones, are unfortunately common and can have severe consequences if left untreated. Due to the rise of antibiotic-resistant bacteria, effective treatments for skin infections must be sought out. Metronidazole and Doxycycline have both been identified as two antimicrobial agents that may provide some relief when treating dermatological infections [1]. Metronidazole is a nitroimidazole antibiotic with bactericidal activity against anaerobic bacteria and some protozoa. It's often used in treating bacterial vaginosis, amebiasis, giardiasis, and trichomoniasis. Doxycycline is a tetracycline antibiotic with broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria as well as some atypical pathogens [2].

Numerous studies have examined the efficacy and safety of Metronidazole and Doxycycline in treating dermatological infections. Unfortunately, there remains a lack of consensus on ideal dose regimens, duration of therapy, or comparative effectiveness between these agents. A systematic review of available literature can help clarify these matters and provide a summary of available evidence regarding their efficacy and safety when treating dermatological infections [3].

This systematic review seeks to assess the efficacy and safety of Metronidazole and Doxycycline for treating dermatological infections. We will assess existing evidence on their use in treating bacterial, fungal, and viral skin infections and provide a critical appraisal of available studies. The outcomes of this review will be relevant for clinicians and other healthcare providers involved with managing dermatological infections; they may even serve to inform future research initiatives and clinical practice.

Brief overview

This systematic review seeks to assess the efficacy and safety of Metronidazole and Doxycycline for treating dermatological infections. Dermatological infections, including bacterial, fungal, and viral ones, can have serious outcomes if left untreated. Metronidazole and Doxycycline have shown promising results in treating these infections; however, details regarding optimal dosage regimens, duration of therapy, and comparative effectiveness remain to be determined [4]. This review will assess the existing evidence on Metronidazole and Doxycycline's effectiveness in treating bacterial, fungal, and viral skin infections and provide a critical appraisal of available studies. The outcomes

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will be pertinent to clinicians and other healthcare providers involved in dermatological infections management; they may even help direct future research efforts or inform clinical practice [5].

A. Background of Metronidazole and Doxycycline

Metronidazole and doxycycline are two well-established antibiotics commonly used in dermatology. Metronidazole, a nitroimidazole compound, was discovered in 1959 and initially prescribed to treat protozoal and anaerobic bacterial infections. Nowadays it's frequently prescribed for various skin conditions like rosacea or acne vulgaris. Doxycycline belongs to the tetracycline antibiotic family and was first developed back in 1960s; since then it has been used for treating various bacterial infections like acne vulgaris, rosacea, Lyme disease etc. [6].

The use of antibiotics in dermatology has seen a marked growth due to their efficacy at treating various skin conditions. Both metronidazole and doxycycline have been thoroughly studied for their efficacy, safety, and potential side effects. This comprehensive review will give an in-depth overview of how metronidazole and doxycycline can be used in dermatological infections, covering their mechanisms of action, indications, dosages, adverse reactions, as well as drug interactions [7].

Prevalence of Dermatological Infections

Dermatological infections are a frequent reason for medical consultations around the world. Skin infections can be caused by various microorganisms such as bacteria, fungi, viruses and parasites; their prevalence varies based on factors like age, geographic location and socioeconomic status. Some of the most prevalent dermatological infections include acne vulgaris, rosacea, impetigo cellulitis tinea and candidiasis [8].

Acne vulgaris, a chronic inflammatory skin condition affecting the pilosebaceous unit, is one of the most prevalent skin conditions globally; up to 85% of adolescents and young adults suffer from it [9]. Rosacea, another common chronic inflammatory skin disorder marked by facial flushing, papules, pustules, and telangiectasias affects around 5% of adult population worldwide. Bacterial infections like impetigo or cellulitis are also quite common - impetigo being highly contagious while cellulitis could potentially lead to severe complications if left untreated [10].

The rise of dermatological infections has created an urgent need for effective treatments. Antibiotics like metronidazole and doxycycline are crucial tools in managing these conditions, attacking the underlying pathogenic microorganisms while relieving symptoms. But proper use of antibiotics during dermatology must be done carefully in order to guarantee successful outcomes and minimize antibiotic resistance risks [11].

II. Metronidazole

Mechanism of Action

Metronidazole is a synthetic nitroimidazole antibiotic and antiprotozoal agent with an unusual mechanism of action. It mainly targets anaerobic bacteria and certain protozoa such as Giardia lamblia, Trichomonasvaginalis, and Entamoebahistolytica [12].

Pharmacologically, metronidazole's mechanism of action involves a series of chemical reactions that eventually result in disruption of bacterial DNA synthesis and cell death. The process can be summed up as follows:

Drug activation

After entering anaerobic bacteria, metronidazole undergoes reduction by the enzyme nitroreductase. This conversion transforms the nitro group (-NO2) of metronidazole into a reactive nitroso group (-NO), producing toxic intermediates like nitroso free radicals [13].

DNA damage

These hazardous intermediates, particularly nitroso free radicals, can bind to bacterial DNA and cause strand breaks and loss of helical structure. Damaged DNA cannot properly replicate, transcribe or repair itself - ultimately leading to cell death in the affected bacteria [14].

Selective toxicity

Metronidazole's mechanism of action is specific for anaerobic bacteria and certain protozoa, since these microorganisms usually possess the nitroreductase enzymes necessary for drug activation. Aerobic bacteria and human cells lack these enzymes, making them less vulnerable to metronidazole's effects [15].

Indications in Dermatology

Rosacea

Metronidazole is often prescribed as the first-line treatment for rosacea due to its effectiveness at decreasing inflammation and improving symptoms. Topical formulations have been the most popular choice, with clinical studies demonstrating significant improvements in erythema, papules, and pustules. In more severe or persistent cases of the condition, oral metronidazole

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may be prescribed in combination with other treatments [16].

Acne Vulgaris

Metronidazole is not typically prescribed as the primary treatment for acne vulgaris, but it may be used as an adjunct therapy when anaerobic bacteria are suspected to have caused the infection. Furthermore, its anti-inflammatory properties could potentially help reduce redness and swelling associated with acne lesions [17].

Perioral Dermatitis

Perioral dermatitis is a skin condition characterized by small, red and inflamed bumps around the mouth. Although its exact cause remains unknown, it has been suggested to be due to an overgrowth of bacteria or yeast. Topical metronidazole has been proven effective in treating this condition with improvements usually seen within a few weeks after beginning treatment [18].

Other Uses

Metronidazole can also be used to treat other skin infections caused by anaerobic bacteria, such as hidradenitissuppurativa--a chronic, inflammatory skin condition affecting hair follicles in areas like armpits and groin. It has also been prescribed off-label for conditions like malodorous ulcerations or wounds where its antimicrobial properties help reduce odor while speeding healing [19].

Dosage and Administration

The dosage and administration of metronidazole depends on the dermatological condition being treated, the severity of the infection, and the patient's overall health. Topical formulations like creams or gels should be applied once or twice daily to the affected area. Oral metronidazole is usually prescribed at a dose of 250-500 mg, two or three times daily depending on infection severity as determined by your healthcare provider [20].

It is essential for patients to adhere strictly to their prescribed treatment regimen in order to achieve optimal results. Following the recommended dosage and administration schedule can reduce the risk of antibiotic resistance while expediting healing. Healthcare providers should monitor patients closely for potential side effects, and make necessary changes in the treatment plan as necessary [21].

Side Effects and Contraindications

Metronidazole is usually well tolerated, with most side effects being mild and transient. Topical formulations may cause local irritation, dryness, redness, or itching; oral metronidazole may cause gastrointestinal side effects like nausea, vomiting, diarrhea or abdominal pain; in rare cases more serious reactions such as peripheral neuropathy, seizures or Stevens-Johnson Syndrome can occur [22].

Metronidazole should not be taken by those with known hypersensitivity to the drug or any nitroimidazole derivatives. Furthermore, those with liver disease should use caution as it is metabolized in the liver and may build up in those with impaired liver function. Furthermore, pregnant and breastfeeding women should refrain from taking metronidazole since its safety during pregnancy and lactation has yet to be fully established [23].

Drug Interactions

Metronidazole may interact with several medications, potentially altering their efficacy or increasing the risk of adverse effects. Some of the most common drug interactions include:

Anticoagulants

Metronidazole may potentiate the anticoagulant effect of warfarin and other coumarin-type anticoagulants, increasing the risk of bleeding. Close monitoring of prothrombin time and appropriate dosage adjustments are necessary when these drugs are used concomitantly [24].

Alcohol

The concurrent use of metronidazole and alcohol may result in a disulfiram-like reaction, causing symptoms such as flushing, headache, nausea, and vomiting. Patients should avoid consuming alcohol during metronidazole treatment and for at least 48 hours after completing therapy [25].

Lithium

Metronidazole may increase lithium concentrations in the blood, potentially leading to lithium toxicity. Patients receiving both drugs should be closely monitored for signs of lithium toxicity, and dose adjustments may be necessary [26].

Cimetidine

Cimetidine may inhibit the metabolism of metronidazole, resulting in increased plasma concentrations and an increased risk of side effects. The use of alternative H2-receptor antagonists, such as ranitidine or famotidine, should be considered in patients receiving metronidazole [27].

Phenytoin and phenobarbital

Anticonvulsant medications may accelerate the metabolism of metronidazole, potentially decreasing its effectiveness. Dosage adjustments may be necessary in order to maintain adequate concentrations of metronidazole.

Healthcare providers must be aware of potential drug interactions when prescribing metronidazole and closely monitor patients for any adverse effects or changes in clinical response. It is

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essential that patients inform their healthcare provider of all medications they take, including prescription drugs, over-the-counter medicines and dietary supplements, so as to minimize the risk of drug interactions [28].

- **DOXYCYCLINE**

Mechanism of Action

Doxycycline is a semi-synthetic tetracycline antibiotic commonly used to treat various bacterial infections, particularly skin-related ones. Its mechanism of action differs from that of metronidazole and targets both aerobic and some anaerobic bacteria. Here we provide an overview of doxycycline's pharmacologically specific mechanism of action [29]:

Protein synthesis inhibition

Doxycycline binds to the 30S ribosomal subunit of bacterial ribosomes, blocking aminoacyl-tRNA attachment to its acceptor site on mRNA-ribosome complex. This action inhibits translation of peptide chains, effectively impairing protein synthesis in bacteria cells [30].

Bacteriostatic effect

Doxycycline's inhibition of protein synthesis is bacteriostatic, meaning it stops bacterial growth and reproduction without directly killing them. As a result, your immune system can more efficiently eliminate remaining bacteria, leading to resolution of your infection [31].

Broad-spectrum activity

Doxycycline is considered a broad-spectrum antibiotic, as it is active against a wide range of Gram-positive and Gram-negative bacteria, including some anaerobes. This broad activity makes it a valuable option for treating various infections, including those caused by mixed bacterial populations [32].

Anti-inflammatory properties

Doxycycline not only has antibacterial activity, but it has anti-inflammatory properties too - making it useful in the treatment of skin conditions like acne and rosacea. Studies have revealed that it inhibits pro-inflammatory cytokines and matrix metalloproteinases responsible for inflammation and tissue damage [33].

Doxycycline's mechanism of action involves inhibition of bacterial protein synthesis and inflammation, making it an effective treatment for various infections such as acne vulgaris, rosacea, and Lyme disease-related skin manifestations [34].

Indications in Dermatology

Acne Vulgaris

Doxycycline is the go-to treatment for moderate to severe acne vulgaris due to its effectiveness at relieving inflammation and targeting bacteria responsible for infection, specifically Propionibacterium acnes. Typically prescribed at a lower dose due to its anti-inflammatory effects, it's often combined with topical treatments like benzoyl peroxide or retinoids [35].

Rosacea

Doxycycline is also prescribed to treat rosacea, particularly when inflammation and papulopustular lesions are present. Doxycycline's anti-inflammatory properties help reduce redness and inflammation associated with this condition. Furthermore, its antimicrobial activity may target bacteria responsible for rosacea's development [36].

Lyme Disease-related Skin Manifestations

Doxycycline is the treatment of choice for early Lyme disease, especially when erythema migrans (the characteristic skin rash) is present. This antibiotic effectively targets Borreliaburgdorferi, the causative bacteria responsible for this illness and prevents its progression into more severe forms [37].

Other Uses

Doxycycline has long been used to treat various skin infections, such as cellulitis, impetigo and folliculitis. Additionally, it's effective at treating certain sexually transmitted illnesses like chlamydia or syphilis which may present with dermatological manifestations [38].

Dosage and Administration

When treating dermatological conditions, the dose and administration of doxycycline depends on the specific condition being treated, the severity of the infection, and patient health. For acne vulgaris and rosacea, lower doses (40-100 mg daily) may be sufficient due to its anti-inflammatory effects [39]. Conversely, in cases of Lyme disease and other bacterial infections requiring higher dosages (100-200 mg daily) to effectively combat causative bacteria.

Doxycycline should always be taken with plenty of water to avoid esophageal irritation or ulceration. To ensure optimal treatment outcomes and minimize antibiotic resistance risks, patients must closely adhere to their prescribed treatment regimen and complete all courses of therapy as instructed [40].

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Side Effects and Contraindications

Doxycycline is generally well tolerated, though some patients may experience side effects such as nausea, vomiting, diarrhea and abdominal pain. Other potential reactions include photosensitivity which could result in sunburn or rash and yeast infections. In rare cases more serious reactions such as drug-induced lupus or Stevens-Johnson syndrome could occur too [41].

Doxycycline should not be taken by those with known hypersensitivity to it or other tetracycline antibiotics. Furthermore, children fewer than 8 should not take it as it may lead to permanent tooth discoloration and enamel hypoplasia. Furthermore, pregnant and breastfeeding women should abstain from using doxycycline since it could harm an unborn child and be excreted in breast milk, potentially harming the infant [42].

Drug Interactions

Doxycycline may interact with several medications, potentially altering their efficacy or increasing the risk of adverse effects. Some of the most common drug interactions include:

Antacids and iron supplements

The concurrent use of doxycycline with antacids or iron supplements may reduce its absorption, leading to decreased efficacy. Patients should take doxycycline at least 2 hours before or after taking antacids or iron supplements to minimize this interaction [43].

Oral contraceptives

Doxycycline may decrease the effectiveness of oral contraceptives, increasing the risk of unintended pregnancy. Women taking doxycycline should consider using an additional form of contraception during treatment and for at least one week after completing therapy [44].

Warfarin

Doxycycline may increase the anticoagulant effect of warfarin, potentially leading to an increased risk of bleeding. Patients taking both drugs should be closely monitored for changes in prothrombin time or international normalized ratio (INR) and appropriate dosage adjustments may be necessary [45].

Penicillin antibiotics

Doxycycline may interfere with the bactericidal activity of penicillin antibiotics, potentially reducing their efficacy. In general, doxycycline should not be administered concurrently with penicillin antibiotics [46].

Retinoids

Doxycycline combined with oral retinoids such as isotretinoin may increase the risk of pseudotumorcerebri, a rare but serious condition marked by increased intracranial pressure. Patients taking both drugs should be closely monitored for symptoms indicative of pseudotumorcerebri, such as headache, visual disturbances or nausea [47].

Healthcare providers must be aware of potential drug interactions when prescribing doxycycline and closely monitor patients for any adverse effects or changes in clinical response. It is essential that patients inform their healthcare provider of all medications they are taking, including prescription drugs, over-the-counter drugs, and dietary supplements, to reduce the risk of drug interactions [48].

Comparative Studies of Metronidazole and Doxycycline

Comparative studies between metronidazole and doxycycline for treating dermatological infections can help healthcare providers decide the most suitable treatment for their patients. Since these antibiotics have distinct mechanisms of action and cover different spectra of bacteria, comparing their efficacy, safety, and tolerability in specific dermatological conditions is imperative. Here are some findings from these comparative studies:

Rosacea

A randomized controlled trial evaluated the efficacy and safety of oral doxycycline (100 mg/day) versus topical metronidazole (1% gel, twice daily) in treating moderate to severe rosacea symptoms. Results showed both treatments significantly improved symptoms; however there was no statistically significant difference between them when it came to efficacy. Nonetheless, those taking doxycycline experienced more gastrointestinal side effects compared to those on metronidazole [49].

Acne vulgaris

A study comparing oral doxycycline (100 mg/day) to topical metronidazole (0.75% gel, twice daily) for treating acne vulgaris found that both treatments led to significant improvements in lesion counts. However, those taking doxycycline experienced greater reductions in both inflammatory and total lesion counts compared to those receiving metronidazole, suggesting doxycycline may be more effective at treating inflammatory acne lesions [50].

Perioral Dermatitis

Unfortunately, few comparative studies have been done between metronidazole and doxycycline for treating perioral dermatitis. Both antibiotics have been reported as effective treatments of this condition; further research is necessary in order to directly compare their efficacy and safety in this regard [51].

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Efficacy in Treating Dermatological Infections

Multiple comparative studies have been conducted to compare the efficacy of metronidazole and doxycycline when treating dermatological infections. Both antibiotics have proven successful at treating various skin conditions, though their individual effectiveness may differ depending on which infection is being addressed [52].

For instance, metronidazole has been proven more effective at relieving rosacea's erythema and papules than doxycycline does when treating its inflammatory component. With acne vulgaris, doxycycline is usually prescribed as the first-line treatment while metronidazole may be added on as an adjunct therapy when anaerobic bacteria are suspected to have contributed to the infection [53].

Tolerability and Safety

Metronidazole and doxycycline tend to have a relatively good tolerance, with most side effects being mild and transient. However, there may be some subtle differences in their safety profiles between the two antibiotics [54].

Metronidazole has a lower risk of photosensitivity compared to doxycycline, making it a safer option for patients with sun sensitivity or living in areas with intense UV exposure. On the other hand, doxycycline may be better suited for use by individuals with liver disease as metronidazole may accumulate due to impaired liver function.

Overall, when selecting between metronidazole and doxycycline for treating a dermatological condition, the patient's medical history, and any potential risks associated with each drug should be taken into consideration [55].

Cost-Effectiveness

When comparing metronidazole and doxycycline for cost-effectiveness, factors like price point, duration of treatment, and efficacy must all be taken into account. On average, metronidazole tends to be less expensive than doxycycline, making it a more cost-effective choice for treating certain skin conditions such as rosacea or perioral dermatitis [56].

Combination Therapy

Rationale for Combining Metronidazole and Doxycycline

Combining metronidazole and doxycycline may be used for treating dermatological infections, particularly when multiple causative factors are present or monotherapy has proven ineffective. The idea behind combination therapy is to take advantage of each drug's distinct mechanisms of action and antimicrobial spectra, potentially providing broader coverage as well as increased efficacy against the causative organisms[57].

For instance, when treating severe acne vulgaris or rosacea where both anaerobic bacteria and inflammation are involved, using metronidazole for its activity against anaerobic bacteria and doxycycline for its anti-inflammatory effects may prove more successful a treatment approach [58].

Studies on the Efficacy of Combination Therapy

Limited studies have been conducted to assess the efficacy of combination therapy with metronidazole and doxycycline for treating dermatological infections. Some results have been promising, with improved clinical outcomes and shorter treatment durations when compared to monotherapy. However, more research is necessary to establish optimal dosing regimens, duration of treatment, and specific indications for this approach [59].

One study demonstrated the efficacy of metronidazole and doxycycline when combined for treating hidradenitissuppurativa, a chronic, inflammatory skin condition characterized by painful nodules and abscesses. The combination therapy led to significant decreases in lesions as well as improvements in patients' quality of life [60].

Potential Side Effects and Drug Interactions

When using combination therapy with metronidazole and doxycycline, it is essential to consider the potential for additive side effects and drug interactions. Some patients may experience an increased risk of gastrointestinal side effects like nausea, vomiting, and diarrhea from taking both antibiotics at once. Furthermore, photosensitivity could be increased when doxycycline is combined with other medications like metronidazole [61].

Drug interactions are always present when taking either metronidazole or doxycycline together, as previously discussed. When taken together, however, the potential risk of interactions may be increased significantly. Therefore, healthcare providers must carefully review a patient's medication history and consider any potential drug interactions when prescribing combination therapy [62].

Resistance

Antibiotic resistance is a serious issue in medicine, particularly dermatology. Resistance develops when bacteria become resistant to antibiotics, rendering them ineffective or inefficient at treating infections. This poses an immediate threat to public health as it could lead to multidrug-resistant strains and decreased treatment options for dermatology

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patients. Here we explore some factors contributing to antibiotic resistance in dermatology as well as its implications when using metronidazole and doxycycline treatments [63].

Prolonged or Inappropriate Antibiotic Use

Prolonged or inappropriate antibiotic usage, particularly when not medically necessary or when given suboptimal doses, can lead to resistance in bacteria. For example, dermatology patients often take antibiotics long term for chronic skin conditions like acne or rosacea. With repeated exposure to antibiotics, bacteria may develop resistance mechanisms such as altering their target site for antibiotics, producing enzymes that inactivate them, or increasing efflux pumps which expel the antibiotic from bacterial cells [64].

Resistance in Acne Vulgaris

Propionibacterium acnes (now known as Cutibacterium acnes) is the main culprit behind acne vulgaris. Unfortunately, antibiotic resistance has become increasingly prevalent within this bacterium, particularly for tetracycline antibiotics like doxycycline. To combat the rising resistance rates, new treatment guidelines have been created which advise limiting antibiotic usage duration and combining antibiotics with topical retinoids or benzoyl peroxide to reduce the likelihood of resistance development [65].

Resistance in Rosacea

Although the exact cause of rosacea remains unclear, certain microorganisms like Demodex mites and some anaerobic bacteria have been suggested as contributing factors. Metronidazole and doxycycline are commonly prescribed medications to treat this condition; though resistance rates tend to be lower than those experienced with acne vulgaris, there remains a potential risk for development of resistance [66].

Importance of Patient Education and Adherence

Patient education and adherence to antibiotic regimens are essential for minimizing antibiotic resistance and achieving optimal treatment results. Healthcare providers should take time to educate patients about proper usage of antibiotics, including the importance of finishing the full course of therapy, potential side effects, and risks associated with antibiotic resistance.

Patients should be encouraged to ask questions and express any worries they have about their treatment, and healthcare providers should be available to address those worries and offer guidance when necessary. By encouraging open communication and providing patient education, healthcare providers can reduce the risk of antibiotic resistance and enhance overall treatment outcomes in dermatology [67].

III. Conclusion

Both metronidazole and doxycycline have an important role in treating various dermatological infections. Each antibiotic has its own specific mechanism of action, indications, as well as potential side effects. While they can be used individually for certain conditions, combination therapy may be necessary to achieve optimal treatment results. It is essential that healthcare providers carefully consider each patient's individual needs and weigh the potential advantages and risks associated with each option before prescribing any therapy.

Furthermore, the growing threat of antibiotic resistance in dermatology emphasizes the significance of proper antibiotic use and patient education. By adopting strategies to minimize resistance development and encouraging patients to adhere to prescribed regimens, healthcare providers can help guarantee these valuable medications continue their efficacy when treating dermatological infections.

Finally, the prudent use of metronidazole and doxycycline, combined with an understanding of their mechanisms of action, indications, and potential interactions is key for providing the most effective and secure treatment for dermatological infections. As research continues to advance our knowledge about these antibiotics and their role in dermatology, healthcare providers must stay informed to ensure the best possible outcomes for their patients.

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