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Griseofulvin: A Comprehensive Review of its Antifungal, Pharmacological, and Clinical Implications

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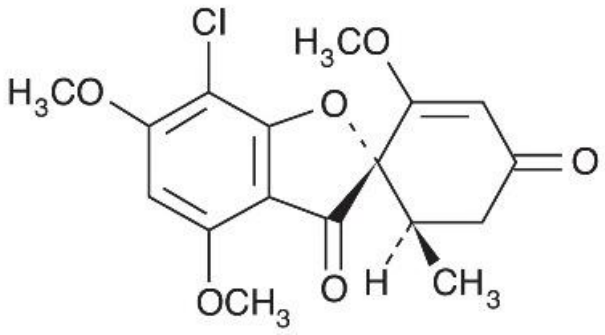
Abstract

Griseofulvin, an antifungal antibiotic, treats fungal infections in humans, animals, and plants. Various Penicillium species produce this compound. Oral administration of griseofulvin is exclusively used for dermatophytosis, as it is ineffective when applied topically. The drug's mechanism of action involves binding to tubulin, which disrupts microtubule function and consequently inhibits mitosis. Industrial production of griseofulvin is achieved through fermentation of the Penicillium Griseofulvin fungus. This review provides an updated overview of the drug, focusing on its mode of action, pharmacokinetics, clinical applications, side effects, drug interactions, patient guidelines, and therapeutic approaches. Additionally, it addresses contraindications

Introduction

Fungal infections present significant treatment challenges, particularly in immunocompromised or neutropenic patients. Most fungi exhibit resistance to conventional antimicrobial agents, and there is a limited availability of drugs for the treatment of systemic fungal diseases [1].
Griseofulvin is a systemic antifungal drug administered orally for the treatment of superficial fungal infections, including dermatophytosis of skin and hair, as well as fungal infections of the nails, scalp, and skin [1].
Griseofulvin demonstrates a wide range of applications, from agriculture to medicine. In agriculture, griseofulvin serves as a crop protectant to prevent fungal colonization and infection [2]. In medicine, griseofulvin has been extensively utilized as an antifungal drug and in treating ringworm and dermatophyte infections in humans and animals [3,4] due to its low toxicity. In cancer research, griseofulvin has exhibited inhibitory effects on cancer cell division and may induce tumor cell death through interaction with the mitotic spindle microtubule [5]. Furthermore, griseofulvin may inhibit hepatitis C virus replication by interfering with microtubule polymerization in human cells [6]. Griseofulvin has long been recognized to cause vasodilation and improve capillary blood flow [7]. Adverse effects of Griseofulvin include headaches, mental confusion, gastrointestinal irritation, photosensitivity, and alterations in liver function. Allergy, headaches, sleep disturbances, and fatigue are common side effects. Griseofulvin is contraindicated in patients with porphyria [1].



Griseofulvin (C17H17ClO6) is a natural product that was first discovered and isolated from Penicillium Griseofulvin in 1939. In addition to Penicillium, griseofulvin may be isolated from other genera of ascomycetes including Xylaria flabelliformis, Abieticola koreana, and Stachybotrys levispora[8.9,10]

In this review article, we summarize the mechanism of action, side effects, drug and food interactions, contraindications, pharmacokinetics, biosynthesis, and chemical synthesis of the antifungal drug griseofulvin.

- The human and animal toxicity of the drug is also discussed.
- The role of green chemistry in sustainable drug discovery

2. Mechanism of action of griseofulvin

Griseofulvin is a microtubule assembly inhibitor. It interferes with microtubule function in dermatophytes to affect the formation of the mitotic spindle. This interference ultimately inhibits mitosis in dermatophytes and may also inhibit the synthesis and polymerization of nucleic acids. Sensitive dermatophytes take up the drug by an energy-dependent mechanism, and resistance can occur via a decrease in this transport.[11]

Through this mechanism, griseofulvin functions as a fungistatic agent against Trichophyton, Microsporum, and Epidermophyton species.[11] It is noteworthy that it is ineffective in treating dimorphic fungi, yeast (Malassezia, Candida), or chromomycosis. Griseofulvin is rapidly eliminated from the body and thus must be administered over an extended period to achieve optimal efficacy.[11]

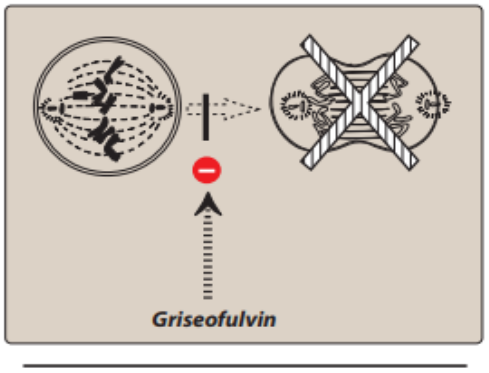


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Figure 1. Inhibition of mitosis by griseofulvin.

3. Pharmacokinetics of Griseofulvin

3.1. Absorption

Griseofulvin is commonly administered orally, although its poor intestinal absorption may lead to treatment failure. A spectrophotofluorometric study demonstrated that griseofulvin absorption and effectiveness are significantly increased with a high-fat diet [11]. Griseofulvin absorption is greatest from the duodenum and least from the stomach, while colon absorption is negligible [12].

3.2. Distribution

Intravenous administration of Griseofulvin results in drug deposition in keratin precursor cells, occurring 4-8 hours after drug administration. The transport of griseofulvin to the stratum corneum appears to be significantly influenced by sweat and transdermal fluid loss. These cells become resistant to fungal invasion because griseofulvin is bound and retained in keratin during differentiation. [13,14]
Skin areas of higher temperature were observed to have higher concentrations of griseofulvin than colder ones, likely due to the medication dissolving in sweat and subsequently being deposited in the horny layer of skin upon sweat evaporation. This also explains the inverse gradient of the drug's concentration in skin, where the highest concentrations are found in the topmost horny layer and the lowest concentrations in deeper layers. [13,14]

3.3. Metabolism and Excretion

The half-life of griseofulvin is 9–21 hours [15]. It undergoes oxidative demethylation and conjugation with glucuronic acid, primarily in the liver; its major metabolite, 6-desmethyl griseofulvin, is microbiologically inactive [15]. Within 5 days, approximately one-third of a single dose of micronized griseofulvin is excreted in the feces, and 50% in the urine, predominantly as glucuronidated 6-desmethyl griseofulvin. The slow penetration rate of griseofulvin into tissues may account for difficulties and delays in eradicating infection in nails [15].

4. Pharmacological uses and medical applications of griseofulvin

4.1. Antifungal application

The initial medical application of griseofulvin was in the treatment of ringworm infections caused by Microsporum canis in guinea pigs [17]. Subsequent investigations revealed its antifungal effect on both Trichophyton and Epidermophyton [18]. Griseofulvin was approved by the Food and Drug Administration (FDA) in 1959, and it remains in use today, considered one of the most widely utilized treatments for dermatophyte fungal infections in humans and animals.

4.2. Non-fungal inflammatory diseases

Further studies have reported the efficacy of griseofulvin in the treatment of non-fungal skin inflammatory diseases, including lichen planus [19] and chronic purpuric dermatosis [20], suggesting potential anti-inflammatory and immunomodulatory properties. Additionally, earlier studies have demonstrated that griseofulvin is effective in treating shoulder-hand syndrome [21], and several other inflammatory, rheumatic conditions, such as posttraumatic reflex dystrophies and scapulohumeral periarthritis [22].

4.3. Cardiovascular applications

It has been demonstrated that intravenous administration of griseofulvin improves coronary blood flow and decreases blood pressure, indicating its peripheral vasodilation effects. Furthermore, griseofulvin increases myocardial heart rate through direct action on the myocardium and vascular smooth muscle rather than via central nervous systems or humoral mechanisms [23,24].

4.4. Antitumor Applications

Griseofulvin has garnered attention for its potential application in cancer chemotherapy due to its low toxicity. In tumor cell lines, the antifungal drug griseofulvin inhibits tumor growth of several forms of cancer cell proliferation by suppressing spindle microtubule dynamics, inducing mitotic arrest, and cell death in multipolar spindles, while not affecting fibroblasts and keratinocytes containing normal centrosome composition. Griseofulvin binds to the αβ intra-dimer tubulin interface and induces mitotic arrest through various mitotic abnormalities, such as misaligned chromosomes and multipolar spindles, resulting in cells containing fragmented nuclei. These cells exhibited increased p53 accumulation in the nucleus, indicating that the cells undergo apoptosis [25,26].

4.5. Antiviral Applications

Griseofulvin has been utilized for zoster-associated pain relief and has been observed to prevent the development of further lesions within two days of initiating treatment [27]. Additional studies have demonstrated that griseofulvin suppresses hepatitis C virus (HCV) replication by

arresting the human cell cycle at the G2/M phase and acting on microtubule polymerization, without

affecting HCV internal ribosome entry site (IRES) dependent translation.

5. Adverse effects of griseofulvin

In general, griseofulvin exhibits few adverse effects. It most commonly causes gastrointestinal issues including nausea, vomiting, epigastric distress, and diarrhea, as well as headache, fatigue, dizziness, insomnia, mental confusion, and impairment of performance of routine activities [28].
A study involving 295 children reported that 79 (or 26.8%) experienced mild to moderate adverse effects, with gastrointestinal issues being the most prevalent. These included elevated triglycerides (1/79), anemia (2/79), SGOT (serum glutamic-oxaloacetic transaminase; 1/79), rash (1/79), abdominal pain (10/79), diarrhea (7/79), dyspepsia (3/79), fever (1/79), headache (12/79), nausea (9/79), weight gain (3/79), vomiting (12/79), and other unspecified events (17/79).[29] All of these adverse effects were transient, and none were classified as severe. There have been post-marketing reports of severe cutaneous and hepatic adverse events associated with griseofulvin use.
Common hypersensitivity reactions may occur, such as cutaneous eruptions, urticaria, and, rarely, angioneurotic edema and erythema multiforme. Peripheral neuropathy and paresthesias of the hands and feet have been reported and may be related to treatment duration.[30] The majority of patients treated with griseofulvin for less than six months experienced improvement or resolution of their neuropathy upon discontinuation of the griseofulvin. Other adverse effects reported occasionally include oral candidiasis.Proteinuria, nephrosis, leukopenia, coagulopathy, hepatitis, elevated hepatic enzymes, hyperbilirubinemia, and gastrointestinal hemorrhage have been reported rarely[28].
Serious adverse effects associated with the use of griseofulvin may include severe cutaneous allergic reactions, facial or lingual edema, urticaria, cutaneous vesicles, hepatic injury, and jaundice.

6. Drug interactions of griseofulvin

6.1. Warfarin

Griseofulvin is an inducer of cytochrome P-450 and thus interacts with medications that metabolize via the P-450 system. One such drug is warfarin. The anticoagulant effect of warfarin can be decreased if griseofulvin is used concurrently. The griseofulvin-warfarin drug interaction is one of the most well-documented warfarin drug interactions. The mechanism of this interaction is unclear. It is commonly believed that griseofulvin enhances the hepatic metabolism of warfarin. The interaction between warfarin and griseofulvin may require up to 12 weeks to fully manifest and may be more significant with the ultramicrocrystalline formulation of griseofulvin. The international normalized ratio (INR) should be monitored closely if griseofulvin is either added to or discontinued from warfarin therapy.[31] Additionally, griseofulvin increases the effects of alcohol and may cause a disulfiram-like reaction.[32]

6.2 Progestins

Case reports of contraceptive failure and menstrual disturbance were reported upon concurrent administration of griseofulvin and combined hormonal contraceptives [33,34,35]. Although there is insufficient evidence to determine whether griseofulvin is teratogenic in humans, it is known to be teratogenic in rats.[36]

6.3. Cyclosporine

Griseofulvin may decrease the level or effect of cyclosporine by altering drug metabolism[37]. Dose readjustment of cyclosporin is recommended in patients with organ transplantation who are concurrently administering cyclosporine and griseofulvin to avoid the possibility of organ rejection.

6.4. Phenobarbital

The hypothesis that phenobarbital sodium interferes with the metabolism of griseofulvin due to its ability to induce hepatic enzymes that increase drug metabolism was tested by a randomized crossover study of six healthy male volunteers who received griseofulvin orally and intravenously, both with and without phenobarbital. The elimination kinetics of griseofulvin for a given subject were identical with or without the administration of phenobarbital; thus, no evidence for enzyme induction was observed. However, the amount of orally administered griseofulvin absorbed with phenobarbital administration was significantly lower than that observed when no phenobarbital was given, suggesting that phenobarbital reduces absorption of the drug.

7. Patient information and therapeutic strategies

Griseofulvin is marketed in several formulations to increase bioavailability and decrease

gastrointestinal intolerance. It is indicated for tinea and other fungal infections, including onychomycosis[40].
Griseofulvin is an oral medication available in microsize (250 and 500 mg tablets) and ultra-micro-size (125 and 250 mg tablets) formulations. The ultra micro-size tablets exhibit superior absorption compared to the microsize formulation. Griseofulvin demonstrates poor water solubility. Optimal absorption from the gastrointestinal tract is achieved when griseofulvin is administered with a high-fat meal.[40] The extended duration of therapy (e.g., 6 to 12 weeks for tinea capitis) may potentially result in non-adherence. A liquid suspension formulation is also available. Each of these medications should be administered daily for the indicated duration and continued until clinical symptoms resolve.

7.1. Dosage & indications

7.1.1. Treatment of tinea cruris and tinea barbae.

Oral dosage (Microsize)
Adults

500 mg PO once daily or divided 2 to 4 times daily until complete eradication of the organism.

Children and Adolescents 3 to 17 years

20 to 25 mg/kg/day (Max: 500 mg/day) PO divided twice daily. Continue treatment until complete eradication of the organism. The FDA-approved labeling states that 10 mg/kg/day PO is typically an effective dose and recommends that children weighing 14 kg to 23 kg receive 125 to 250 mg/day PO and that children weighing more than 23 kg receive 250 to 500 mg/day PO in divided doses.

Oral dosage (Ultramicrosize)
Adults

375 mg PO administered either once daily or divided 3 times daily until complete eradication of the organism.
Children and Adolescents 3 to 17 years
10 to 15 mg/kg/dose (Max: 375 mg/dose) PO once daily. Continue treatment until complete eradication of the organism. The FDA-approved labeling states that 7.3 mg/kg/day PO is typically an effective dose and recommends that children weighing 16 kg to 27 kg receive 125 to 187.5 mg/day PO and that children weighing more than 27 kg receive 187.5 to 375 mg/day PO.

7.1.2. Treatment of tinea pedis

Oral dosage (Microsize)
Adults

750 to 1,000 mg PO once daily or divided 2 to 4 times daily for 4 to 8 weeks or until complete eradication of the organism.
Children and Adolescents 3 to 17 years
20 to 25 mg/kg/day (Max: 1 g/day) PO divided twice daily. Administer for 4 to 8 weeks or until complete eradication of the organism. The FDA-approved labeling states that 10 mg/kg/day PO is typically an effective dose and recommends that children weighing 14 to 23 kg receive 125 to 250 mg/day PO and that children weighing more than 23 kg receive 250 to 500 mg/day PO in divided doses.

Oral dosage (Ultramicrosize)
Adults

750 mg PO once daily or divided 2 to 3 times daily for 4 to 8 weeks or until complete eradication of the organism.
For individuals aged 3 to 17 years:
Administer 10 to 15 mg/kg/dose (not exceeding 375 mg/dose) orally once per day for a minimum of 6 weeks or until the organism is fully eliminated. The FDA-sanctioned dosage is 7.3 mg/kg/day orally, with 125 to 187.5 mg/day or 187.5 to 375 mg/day for children weighing 16 to 27 kg or over 27 kg, respectively.

7.1.3. Treatment of tinea corporis

Oral administration (Microsize)
For adults

Give 500 mg orally once daily or split into 2 to 4 doses daily for 2 to 4 weeks or until the organism is completely eradicated.
For individuals aged 3 to 17 years:
Administer 20 to 25 mg/kg/day (not exceeding 500 mg/day) orally, divided into two doses. Continue treatment for 2 to 4 weeks or until the organism is fully eliminated. FDA-approved guidelines indicate that 10 mg/kg/day orally is typically effective and suggest that children weighing 14 kg to 23 kg receive 125 to 250 mg/day orally, while those weighing over 23 kg receive 250 to 500 mg/day orally in divided doses.

Oral administration (Ultramicrosize)
For adults

Provide 375 mg orally once daily or split into 3 doses daily for 2 to 4 weeks or until the organism is completely eradicated.

For individuals aged 3 to 17 years

Give 10 to 15 mg/kg/dose (not exceeding 375 mg/dose) orally once daily. Continue treatment for 2 to 4 weeks or until the organism is fully eliminated. FDA-approved guidelines state that 7.3 mg/kg/day orally is typically effective and recommend that children weighing 16 kg to 27 kg receive 125 to 187.5 mg/day orally, while those weighing over 27 kg receive 187.5 to 375 mg/day orally.

7.1.4. Treatment of tinea unguium (onychomycosis)

Oral administration (Microsize)
For adults:

Administer 750 to 1,000 mg orally once daily or split into 2 to 4 doses daily for at least 4 months, depending on growth rate.

For individuals aged 3 to 17 years

Give 20 to 25 mg/kg/day (not exceeding 1 g/day) orally, divided into two doses. Continue treatment for at least 4 months, depending on growth rate. FDA-approved guidelines indicate that 10 mg/kg/day orally is typically effective and suggest that children weighing 14 to 23 kg receive 125 to 250 mg/day orally, while those weighing over 23 kg receive 250 to 500 mg/day orally in divided doses.

Oral administration (Ultramicrosize)
For adults

Provide 750 mg orally once daily or split into 2 to 3 doses daily for at least 4 months, depending on growth rate.

For individuals aged 3 to 17 years

Administer 10 to 15 mg/kg/dose (not exceeding 750 mg/dose) orally once daily. Continue treatment for at least 4 months, depending on growth rate. FDA-approved guidelines state that 7.3 mg/kg/day orally is typically effective and recommend that children weighing 16 kg to 27 kg receive 125 to 187.5 mg/day orally, while those weighing over 27 kg receive 187.5 to 375 mg/day orally.

7.1.5. Treatment of toenail

Dosage Instructions for Oral Administration (Microsize)
For Adults

Administer 750 to 1,000 mg orally once daily or split into 2 to 4 doses throughout the day for a minimum of 6 months, adjusting based on growth progression.

For Children and Adolescents (3 to 17 years)

Prescribe 20 to 25 mg/kg/day (not exceeding 1 g/day) orally, divided into two doses. Continue treatment for at least 6 months, depending on growth rate. FDA-approved guidelines suggest 10 mg/kg/day orally as typically effective, recommending 125 to 250 mg/day for children weighing 14 to 23 kg, and 250 to 500 mg/day for those over 23 kg, administered in divided doses.

Dosage Instructions for Oral Administration (Ultramicrosize)
For Adults

Prescribe 750 mg orally once daily or divided into 2 to 3 doses throughout the day for a minimum of 6 months, adjusting based on growth progression.

For Children and Adolescents (3 to 17 years)

Administer 10 to 15 mg/kg/dose (not exceeding 750 mg/dose) orally once daily. Continue treatment for at least 6 months, depending on growth rate. FDA-approved guidelines suggest 7.3 mg/kg/day orally as typically effective, recommending 125 to 187.5 mg/day for children weighing 16 kg to 27 kg, and 187.5 to 375 mg/day for those over 27 kg.

8. Maximum Dosage Guidelines

8.1. Adults and Geriatric Patients

Do not exceed 1 g/day orally for microsize griseofulvin or 750 mg/day for ultramicrosize griseofulvin.

Adolescents

FDA-approved dosage for microsize griseofulvin is 10 mg/kg/day orally (maximum 500 mg/day), though off-label use up to 25 mg/kg/day orally (maximum 1 g/day) has been reported. For ultramicro size griseofulvin, the FDA-approved dosage is 7.3 mg/kg/day orally (maximum 375 mg/day), with off-label use up to 15 mg/kg/day orally (maximum 750 mg/day) reported.

Children (3 to 12 years)

The same dosage guidelines as adolescents apply.

Children (1 to 2 years), Infants, and Neonates

Safety and efficacy have not been established.

9. Dosing Considerations

9.1. Hepatic Impairment

Specific dosage adjustments are not provided. Use cautiously in patients with hepatic impairment due to hepatic metabolism. Contraindicated in hepatocellular failure.

9.2. Renal Impairment

No dosage adjustment is necessary.

10. Administration Guidelines

Oral Administration

Bioavailability varies between microsize and ultramicro-size formulations and manufacturers.
Ultramicrosize Griseofulvin Tablets:
Take orally with a fatty meal to enhance absorption. Tablets may be swallowed whole or crushed and mixed with a tablespoon of applesauce, to be swallowed immediately without chewing.
Microsize Griseofulvin Tablets and Suspension:
Take orally with a fatty meal to enhance absorption. For suspension, shake well before use.

Monitoring

Healthcare providers who prescribe griseofulvin might be concerned about checking alanine aminotransferase (ALT), aspartate aminotransferase (AST), and complete blood count (CBC) with differential. A comprehensive retrospective study involving adults and children taking griseofulvin for dermatophyte infections was conducted. The research revealed a minimal occurrence of abnormal laboratory test results. The majority of these abnormalities were minor and did not necessitate

stopping the medication or additional laboratory testing. Increases in ALT and AST, as well as instances of anemia, lymphopenia, and neutropenia, were rare and similar to baseline abnormality rates. These findings suggest that regular laboratory tests are unnecessary for both adults and children using griseofulvin to treat dermatophyte infections.[71]

11. Storage

Keep this medication at a controlled room temperature (between 68 and 77 degrees F.) Shield the medication from light. Avoid storing the tablets in damp or humid areas such as bathrooms.

12. Contraindications

12.1. Hepatic disease

Griseofulvin is not recommended for patients with liver failure and should be used with caution in those with other liver conditions. The drug is metabolized by the liver, and its use has been linked to cases of liver toxicity (e.g., jaundice, elevated liver enzymes, and high bilirubin levels). Regular assessment of both liver and kidney function is advised during griseofulvin treatment[42].

12.2. Carbapenem hypersensitivity, cephalosporin hypersensitivity, penicillin hypersensitivity

Griseofulvin should not be given to patients with a known hypersensitivity to the drug. This sensitivity can manifest as hives, various rashes, and in rare cases, angioedema and serum sickness-like reactions. As griseofulvin is derived from a Penicillium species, there is a theoretical risk of cross-sensitivity in patients allergic to penicillin. However, penicillin-allergic patients have been treated with griseofulvin without adverse effects. Similar precautions may apply to those with cephalosporin or carbapenem allergies due to the structural similarities between these antibiotics and penicillin [39].

12.3. Systemic lupus erythematosus (SLE)

Individuals with systemic lupus erythematosus (SLE) or similar conditions should carefully consider the potential benefits and risks before using griseofulvin, as it has been known to worsen lupus symptoms [43].

12.4. Sunlight (UV) exposure

There have been reports of photosensitivity reactions during griseofulvin therapy. Patients should limit their exposure to intense natural or artificial sunlight. The use of protective clothing and sunscreens is recommended[39].

12.5. Porphyria

Griseofulvin is contraindicated in patients with porphyria. The medication interferes with porphyrin metabolism, and long-term use can lead to increased porphyrin levels in both feces and red blood cells. This may trigger an acute intermittent porphyria attack in susceptible individuals [41].

12.6. Pregnancy

Due to potential teratogenic and abortifacient effects, griseofulvin use during pregnancy is contraindicated. Since 1977, two cases of conjoined twins have been reported following griseofulvin use in the first trimester of pregnancy. FDA surveillance identified griseofulvin as the sole maternal drug exposure in both instances. Some pregnant women using the drug have experienced spontaneous abortions in addition to congenital abnormalities. An examination of 4,264 spontaneous abortions from 1980 to 1983 showed that 7 women had griseofulvin exposure within the previous 3 months (RR = 2.5, 95% CI 1.01, 6.1). Women who are pregnant or may become pregnant should be informed about the potential fetal risk. Women should be directed to use effective contraception during and for 1 month after completing griseofulvin treatment. Men are advised to wait 6 months post-treatment before attempting to father a child. It's worth noting that concurrent use has been shown to decrease oral contraceptive effectiveness[39].

12.7. Breast-feeding

Limited information is available regarding griseofulvin use during lactation, and its excretion in human breast milk is unknown. Due to potential adverse effects on nursing infants, its use is not recommended for breastfeeding mothers [44].

12.8. Serious rash

Griseofulvin treatment has been linked to severe dermatologic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme. Some of these adverse events may lead to hospitalization or death [39].

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