Review article

Isoconazole nitrate: a unique broad-spectrum antimicrobial azole effective in the treatment of dermatomycoses, both as monotherapy and in combination with corticosteroids

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Summary

Fungal skin infections, or dermatomycoses, are associated with a broad range of pathogens. Involvement of gram-positive bacteria is often suspected in dermatomycoses. Inflammation plays an important role in dermatomycoses, displaying a close association between frequent inflammation and reduced skin-related quality of life. Isoconazole nitrate (ISN) is a broad-spectrum antimicrobial agent with a highly effective antimycotic and gram-positive antibacterial activity, a rapid rate of absorption and low systemic exposure potential. ISN is effective against pathogens involved in dermatomycoses, with minimum inhibitory concentrations well below the concentration of ISN in skin and hair follicles. The combination of the corticosteroid diflucortolone valerate with ISN (Travocort®) increases the local bioavailability of ISN. Compared with ISN monotherapy, Travocort has a faster onset of antimycotic action, faster relief of itch and other inflammatory symptoms, improved overall therapeutic benefits and earlier mycological cure rate. Travocort is effective in the treatment of inflammatory mycotic infections, and also in the eradication of accompanied gram-positive bacterial infections. The rapid improvement observed with Travocort treatment, combined with favourable safety and tolerability, results in higher patient satisfaction, and therefore, can be an effective tool to increase treatment adherence in patients with dermatomycoses accompanied by inflammatory signs and symptoms.

Key words: isoconazole nitrate, diflucortolone valerate, mycoses, antifungals, Travocort, Travogen

Introduction

Widespread utility of antifungals

Dermatophytoses, commonly known as ringworm or tinea, are superficial fungal infections caused by dermatophytes, a group of keratinophilic fungi that infect the skin, hair and nails.[1] Dermatophyte infections are extremely common and are estimated to affect more than 20 –25% of the world's population, and their prevalence is increasing.[2,3] In most cases, management of the infection with a topical antifungal agent is effective using one of the two main classes: azoles and allylamines.[4,5] The azoles are the most widely used antifungal drugs.[4] Azoles act primarily by inhibiting the fungal cytochrome P450 enzyme (CYP450), 14α-demethylase. There are two groups of azoles in current clinical use: the imidazoles, which have a two-nitrogen azole ring and are predominantly used topically (isoconazole, bifonazole, clomidazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole, tioconazole) and the triazoles, which have three nitrogens in the azole ring and are primarily used for systemic administration (fluconazole, itraconazole, voriconazole, and fosfluconazole, posaconazole, terconazole).[4,6]

Recently, a systematic review of 104 randomised controlled studies (N = 15 795) evaluated the efficacy of 16 topical antifungal agents vs. placebo in the

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treatment of cutaneous candidiasis and tinea versicolor, tinea corporis, tinea cruris and tinea pedis.[7] A pooled subanalysis of mycological cure rate efficacy ($N = 3044$) demonstrated the consistent superiority of topical azoles over placebo, with an estimated pooled odds ratio of 10.25 (95% CI 6.88–15.27) favouring azoles. Moreover, no differences were found in safety and tolerability in all direct comparisons made between antifungals and placebo or among antifungal classes. The results of this meta-analysis justify the use of topical antifungal drugs over placebo, irrespective of the drug evaluated, pharmacological class, dosages, concentration, therapeutic regimen adopted, duration of the treatment, diagnosed dermatomycosis and efficacy outcome taken into consideration.

Isoconazole nitrate

Isoconazole nitrate (ISN) belongs to the azole class of antifungal agents and is the active ingredient in the topical drugs Travocort® and Travogen® (Bayer HealthCare/Intendis GmbH), which were specifically developed to treat superficial fungal diseases. Based on its molecular structure, (*RS*)-1-[2-[(2,6-dichlorobenzyl) oxy]-2-(2,4-dichlorophenyl)ethyl]-1*H*-imidazole) ISN belongs to the N-substituted imidazole group of azoles, and is closely related to miconazole (Table 1).[8]

Antimicrobial properties of isoconazole nitrate

The most common pathogens relevant in superficial fungal infections are dermatophytes (~70%), yeasts (~35%), and non-dermatophytic moulds (<10%).[2,9–16] Most dermatophytoses involve more than one type of pathogen from the *Trichophyton*, *Microsporum* or *Epidermophyton* species.[2,3,17] In addition, dermatomycoses are often accompanied by bacterial superinfections, which can be caused by a mixture of different bacteria, but most often involve bacteria belonging to the *Staphylococcus* spp.[17,18] Therefore, from a clinical point of view, there is a need for an antimicrobial treatment that is effective across a broad spectrum of pathogens, and displays both antifungal and antibacterial activity. ISN has a broad spectrum of antimicrobial activity against dermatophytes, pathogenic yeasts (including the causative organism of pityriasis versicolor),

Table 1 Molecular characteristics of isoconazole nitrate.

Characteristic	Description	Reference
Isoconazole nitrate		
Molecular structure	((RS)-1-[2-[(2,6-dichlorobenzyl)oxy]-2 -(2,4-dichlorophenyl)ethyl]-1H-imidazole)	[43]
Molecular formula	$C_{18} H_{14} Cl_4 N_2O$	[43]
Main metabolites	2,4-Dichloromandelic acid and 2-(2,6-dichlorobenzyloxy)-2 -(2,4-dichlorophenyl)-acetic acid	
Physicochemical parameters		
pKA	6.68	[81]
Log P	5.6	[81]
Spectrum of activity	Dermatophytes, pathogenic yeasts, pathogenic filamentous fungi, gram-positive bacteria and trichomonads	[82]
Formulation for topical use	Travogen 1% w/w isoconazole nitrate (10 mg g^{-1}) cream (white to faintly yellow) for topical use Travocort 1% w/w isoconazole nitrate (10 mg g^{-1}) and 0.1% w/w diflucortolone valerate (1 mg g^{-1}) cream (white to faintly yellow) for topical use	[61]
Molecular structure		

Isoconazole nitrate

filamentous fungi, moulds, gram-positive bacteria such as *Corynebacterium minutissimum*, the causative organism of erythrasma[8,19,20] (Table 2 and Table 3).

Spectrum of clinical antifungal action

The broad antifungal efficacy of ISN has been demonstrated in numerous clinical investigations. In patients with dermatomycoses, caused by dermatophytes like *Microsporum* spp., *Trichophyton* spp., *Epidermophyton* spp., *Candida albicans,* and other species (*Malassezia furfur*), monotherapy with 1% ISN cream, solution or spray, either once or twice daily resulted in cure rates ranging from 96 to 100%.[21] Furthermore, in 54 patients with tropical dermatomycoses (one patient with a dermatomycosis caused by *Trichosporum beigelii*

and one by *Geotrichum candidum*), clinical and mycological cure was observed in 47 of the 49 patients treated with 1% ISN cream: 29 patients were cured in 3–4 weeks, 15 patients in 5–6 weeks and 3 patients in 8 weeks.[22] In another study, coal miners with toenail and foot infections due to *Hendersonula toruloidea*, *Scytalidium hyalinum* and dermatophytes such as *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum* were treated with 1% ISN cream. Clinical cure rate was 80% after 6 weeks of treatment.[23]

Antifungal activity *in vitro*

Results of *in vitro* studies have helped explain the highly effective clinical antifungal profile of ISN. Table 2

Table 2 Antimycotic action of isoconazole nitrate.[69]

Class of microorganism	Species	Minimum inhibitory concentration (MIC) (µg ml^{-1})[69]	Isoconazole nitrate concentration in the stratum corneum 1 h after topical application[26]
Dermatophytes	*Trichophyton mentagrophytes*	0.4	2500–3500 µg ml^{-1}
	Trichophyton rubrum	0.2	
	Microsporum gypseum	1.6	
	Microsporum canis	0.8	
	Epidermophyton floccosum	1.6	
Yeasts	*Candida albicans*	6.3	
	Candida albicans (isolate 130)	0.12–4 [83]	
	Candida parapsilosis	1.6	
	Candida krusei	3.1	
	Torulopsis glabrata	6.3	
Moulds	*Aspergillus fumigatus*	0.8	
	Aspergillus flavus	6.3	
	Aspergillus niger	0.4	

Table 3 Summary of the minimal inhibition concentration (MIC) of isoconazole nitrate for different gram-positive bacteria.

Gram-positive bacteria	Kessler *et al.* [8] MIC (µg ml^{-1})	Czaika *et al.* [20] MIC (µg ml^{-1})	Isoconazole nitrate concentration in the stratum corneum 1 h after topical application[26]
Staphylococcus aureus	6.3	18	2500–3500 µg ml^{-1}
MR *Staphylococcus aureus*		32	
Staphylococcus epidermidis		6	
Staphylococcus haemolyticus		24	
Staphylococcus hominis		15	
Streptococcus salivarius		3	
Streptococcus viridans (M±σ)			
Staphylococcus faecalis	50.0		
Staphylococcus/Micrococc. species	3.1		
Bacillus cereus		19	
Corynebacterium tuberculostearicum		4	
Propionibacterium acnes		16	

MIC = minimal inhibitory concentration; MR = methicillin resistant.

depicts the *in vitro* inhibition activity of ISN across a broad spectrum of fungal pathogens.[24] The antifungal activity of topical ISN can in part be caused by the concentrations of ISN remaining in the skin after application, which far exceeded the minimal inhibitory concentration (MIC) values of ISN against dermatophytes, yeasts and moulds.[24,25] At 1 h after topical application of 1% ISN, the active ingredient was reported at median concentrations of $3500 \ \mu g \ ml^{-1}$ in the stratum corneum (SC), $20 \ \mu g \ ml^{-1}$ in the epidermis and $3 \ \mu g \ ml^{-1}$ in the dermis.[26] To put this in perspective, the MIC of ISN ranged from 0.2 to $1.6 \ \mu g \ ml^{-1}$ for dermatophytes, 1.6 to $6.3 \ \mu g \ ml^{-1}$ for yeasts and 0.8 to $6.3 \ \mu g \ ml^{-1}$ for moulds, depending on the species (Table 2).[24]

Bimodal antifungal action

Isoconazole nitrate exhibits fungistatic activity that arrests fungal growth by targeting the biosynthesis of some integral components of the fungal cell membrane (not present in human cells). Similar to other clinically relevant imidazoles, ISN inhibits the 14α-demethylation of lanosterol, thereby blocking the synthesis of ergosterol (Fig. 1). In some fungal species, it also blocks the subsequent $\Delta22$-desaturase step. Ergosterol plays a key role in the integrity of the fungal cell membrane; therefore, by blocking the synthesis of ergosterol and replacing it with other sterols, the normal function of the fungal membrane is altered.[27] Both the depletion in ergosterol and the accumulation of lanosterol-like sterols lead to defective cell membranes, resulting in defective cell budding and enlargement.[28] The consequent accumulation of lanosterol induces permeability changes, membrane leakage, changes in nutrient transport and inactivity of membrane-bound enzymes, inhibition of growth, increased susceptibility to host-defence mechanisms, and eventually cell death.[29,30] Isoconazole nitrate also exerts several other effects on the fungal membrane, which are independent of

inhibition of the ergosterol synthesis.[31,32] ISN caused a rapid reduction of cellular adenosine triphosphate (ATP) within 10 min of *in vitro* exposure.[33,34] At low concentrations (1, $10 \ \mu g \ ml^{-1}$), ISN induced a blockade of cell division *in vitro* by its action on synthesis and organisation of the cell membrane. At higher concentrations (50, $100 \ \mu g \ ml^{-1}$; but those still lower than the concentrations observed in the skin after application of 1% ISN), ISN induced necrosis and death of fungal cells.[35–37]

An additional antifungal mechanism of azoles involves the accumulation of drug-induced reactive oxygen species (ROS) within the fungal organism, resulting in oxidative damage and cell death.[38] An increase in the ROS has been reported as an additional mode of action for miconazole, a molecule structurally similar to ISN.[39–41] Moreover, ISN and miconazole have very similar modes of action, not only against dermatophytes and yeasts but also against bacteria.

Antibacterial properties of isoconazole nitrate

Bacterial superinfections in dermatomycoses

Dermatomycoses are often accompanied by bacterial superinfections. Bacterial superinfections in dermatomycoses are often caused by a mixture of different bacteria; however, *Staphylococcus aureus* and an increasing number of its methicillin-resistant species (MRSA) play a key role in this condition.[18] For example, long-standing fungal infections, particularly those affecting the feet, are commonly co-infected by a large number of staphylococci, which are thought to play a pathogenetic role in the perpetuation of the lesion by sustaining the tissue abnormalities.[42] Therefore, from a clinical standpoint, an antifungal agent with additional antibacterial activity is a therapeutic advantage in treating dermatomycoses with a suspected bacterial superinfection.
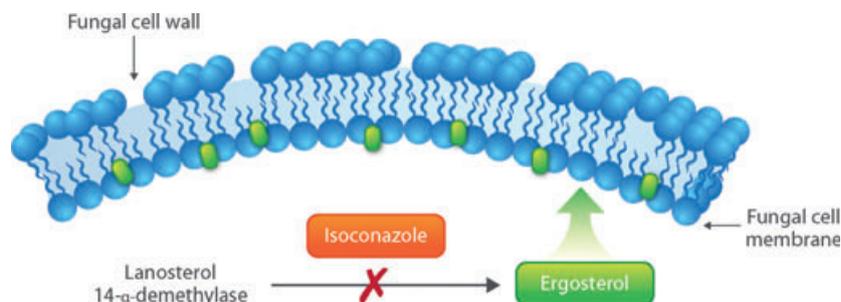

Figure 1 Antimycotic mechanism of action of isoconazole nitrate.[35]

Spectrum of clinical antibacterial action

The antibacterial efficacy of ISN was first demonstrated by Wendt and Kessler.[43] After the application of isoconazole-free base, ISN (1%) cream and vehicle cream onto human skin, a more significant reduction in the number of bacteria was observed after application of the ISN cream vs. vehicle cream (Table 4). ISN is effective in treating erythrasma caused by the gram-positive *C. minutissimum*[44], further demonstrating the efficacy of ISN against gram-positive bacteria. Tinea pedis interdigitalis (athlete's foot), a common fungal infection in adults, presents with dermatophytes as causative pathogens. However, more severe presentations involve a malodour in the skin between the toes that may be associated with colonisation by bacteria such as *Micrococcus sedentarius*, *C. minutissimum* and *Brevibacterium epidermidis*.[45,46]

Antibiotic use is a driving factor in the threat of increasing bacterial resistance among animals and humans.[47] Because ISN is an antimicrobial agent and not a conventional antibiotic, exposure to ISN does not contribute to development of antibiotic resistance.

Antibacterial activity *in vitro*

Kessler and colleagues were the first to investigate the antibacterial potential of ISN *in vitro* (Table 3).[24] The investigators reported a low MIC for *S. aureus*, but they could not determine an MIC for other gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris* and *Pseudomonas aeruginosa*. From these results, the authors concluded that ISN has a bacteriostatic effect on gram-positive bacteria, but not on gram-negative bacteria. In addition, an antibacterial effect of ISN on *Helicobacter pylori* has been described.[48]

Results from a more recent study showed a bacteriostatic and bactericidal action of ISN against a broader range of potentially pathogenic bacterial species such as *S. aureus*, *Staphylococcus haemolyticus*, *Propionibacterium acnes* and *Corynebacterium tuberculostearicum*. Interestingly, ISN was also effective in inhibiting a multi-drug-resistant *S. aureus* strain (MRSA).[20]

Mode of antibacterial action: ROS

Data presented by Czaika and colleagues (this issue) suggest that, like the antifungal mechanism of ISN, the bacteriostatic and bactericidal action of ISN against gram-positive bacteria may also involve an increase in ROS (Fig. 2).[20] The elicitation of increased ROS concentration within bacteria results in oxidative stress that causes damage to internal cell structures, eventually leading to apoptosis and cell death. *Staphylococcus aureus* produces a membrane-bound antioxidant, or carotenoid, that protects against ROS released by host macrophages.[49] Based on a significant increase in cells testing positive for ROS, this study suggested that ISN passed through the protective coating of *S. aureus* and induced cell death by generating ROS inside the cell[20] Similarly, miconazole is known to elicit an increase in ROS, leading to lethal cell damage.[20,50,51]

Pharmacokinetic profile of isoconazole nitrate

Cutaneous absorption

For imidazoles, it has been shown that a lower molecular weight results in a higher lipophilicity, which in

Table 4 Bacterial titre on the skin after treatment with isoconazole nitrate (log/cm^3).[45]

Formulation	Median	Quartile		Significance
	Q$_{50}$	Q$_{25}$	Q$_{75}$	
TS-cream base	6.22	5.99	6.54	$P \leq 0.01$
Isoconazole nitrate 1% in TS-cream base	3.82	3.03	4.79	

TS-cream base was an oil–water emulsion consisting of Tween® 60 and Span® 60.
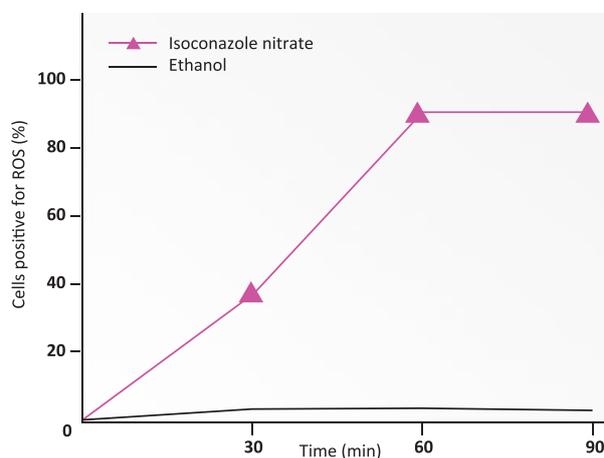

Figure 2 Induction of reactive oxygen species (ROS) in *Staphylococcus aureus*. Cells (strain DSM 2569) were stained with reactive oxygen sensor green reagent before, 30 and 60 min after treatment with isoconazole nitrate. The relative number of reactive oxygen sensor green positive stained cells is given.[20]

turn, leads to increased membrane penetration and sustained contact with its inhibition target, membrane-bound 14α-demethylase.[42] ISN shares this favourable pharmacokinetic characteristic. ISN rapidly penetrates human skin, reaching maximum concentration in the SC and the dermis as soon as 1 h post-application (Fig. 3). In injured skin, local concentration of ISN cream was approximately five times higher.[26] ISN also penetrated more rapidly into the skin compared with other azoles, such as econazole nitrate.[26,52]

When applied topically, active concentrations of ISN in the skin are relatively long-lasting. ISN concentrations were several magnitudes higher than the MICs for skin dermatophytes for up to 7 days postadministration.[53] ISN concentrations were still detectable in the skin up to 2 weeks after the last application.[24,25]

Recently, Lademann and colleagues reported that hair follicles, which can serve as deposits for residual infectious materials,[54–57] also function as long-term reservoirs for topically applied ISN. This is clinically relevant for cases where a long-lasting therapeutic effect beyond the application time is required; for example, to prevent re-infection.[25] In their investigations on 10 healthy volunteers, the ratio between ISN concentration in the SC and in the hair follicle was 7 : 3 at 6 h after end of treatment. However, at 1 week post-treatment, approximately equal amounts of the substance were recovered from the hair follicle and the SC, indicating a shift in the distribution of the drug within the skin (Fig. 4). The authors suggest that the hair follicle acts as a reservoir for ISN that protects against textile contact, washing and desquamation.
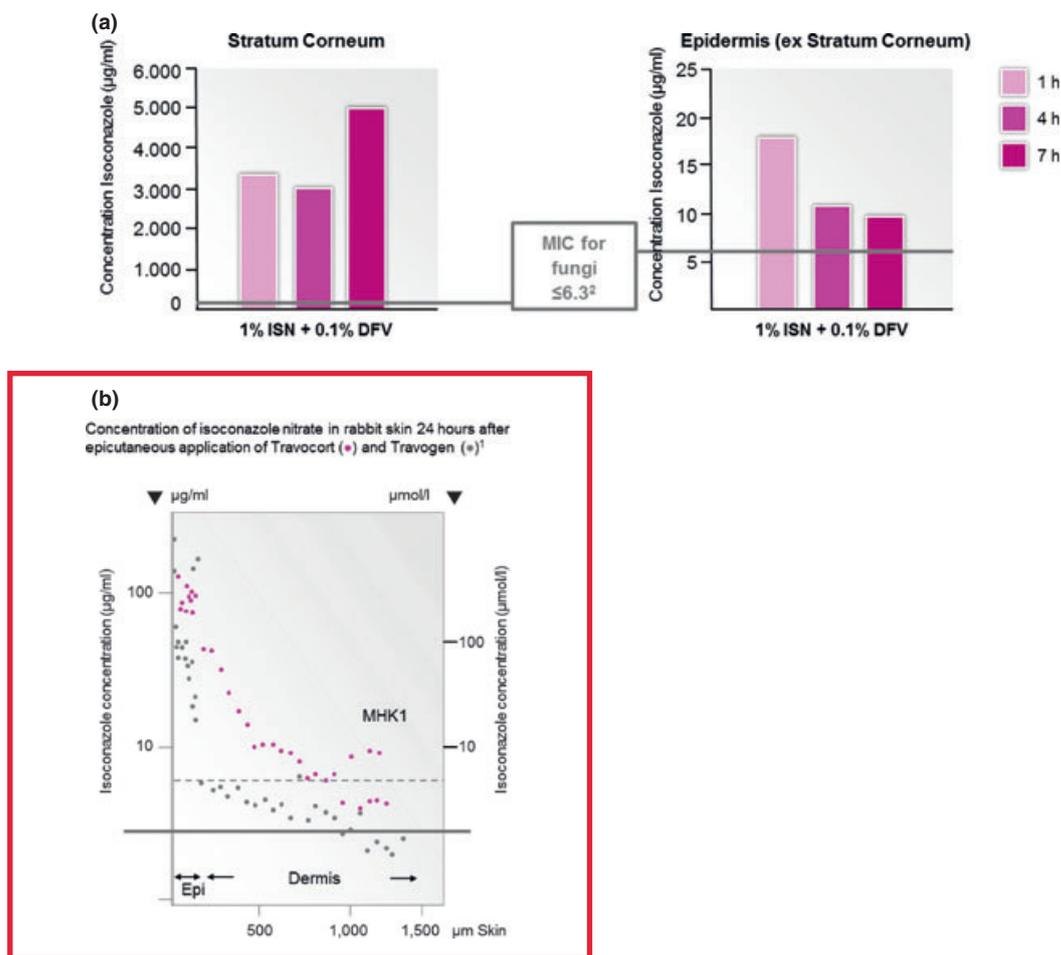

Figure 3 Average concentration of H³ isoconazole in human skin after application with diflucortolone-21-valerate (applied dose 12 mg cream/2 cm² skin),[26,69] with high concentrations of isoconazole achieved in the stratum corneum and epidermis only 1 h after application (a).[26] Concentration of isoconazole nitrate in rabbit skin 24 h after epicutaneous application of Travocort and Travogen (b).

Low systemic exposure

Systemic exposure of ISN due to percutaneous absorption is low. Even after removal of the horny layer, less than 1% of the applied dose reached the systemic circulation within 4 h, a level of absorption that was consistent with that of other imidazoles.[52,58–60] The percutaneous portion of ISN was too low for analysis of metabolism and excretion; therefore, a radiolabelled isotope of ISN was generated and injected into healthy volunteers. ^{3}H-labelled ISN was completely metabolised and rapidly eliminated, yielding 2,4-dichloromandelic acid and 2-(2,6-dichlorobenzyloxy)-2-(2,4-dichlorophenyl)-acetic acid as main metabolites. One-third and two-thirds of the labelled ISN was excreted with the urine and bile, respectively. Within 24 h, 75% of the total ^{3}H-ISN dose was excreted.[61]

Enhancing results through combination of isoconazole with topical corticosteroids

In dermatomycoses, the fungal pathogen invades the SC and produces the exo-enzyme keratinase, inducing an inflammatory reaction at the site of infection.[62–65] The chief symptoms of tinea infections are itch, burning and general irritation of the skin largely associated with the body's inflammatory response to the fungal pathogen. Depending on the precise fungal aetiology, these symptoms can be particularly pronounced. Customary signs of inflammatory reactions include erythema (ruber), swelling (induration), and heat and alopecia (loss of hair) at the site of infection.[66] However, itch is the dominant symptom and can lead to severe pruritus that may progress to pain when persistent scratching leads to maceration and the development of a secondary bacterial infection. Therefore, treatment of the inflammatory component of fungal infections is paramount to ensuring an effective clinical strategy.

Topical corticosteroids are a standard treatment approach for many skin diseases[67] primarily due to their anti-inflammatory, vasoconstrictive, anti-proliferative and immunosuppressive properties.[68] In addition to the primary fungal infection, dermatomycoses are often associated with a major symptomatic burden: inflammation, pruritus (itching), burning sensation and erythema.[69,70] The key advantage of combining a topical antifungal treatment with a topical corticosteroid is that the latter promotes the rapid resolution of signs and symptoms, and hence, rapid relief for the patient.[71] This helps restore normal skin conditions while a healthy microbial flora is established, and is likely to encourage patient adherence to treatment.

Diflucortolone valerate

Diflucortolone valerate (DFV) is the second active ingredient in Travocort, along with ISN, and is a class III corticosteroid with low systemic absorption.[72] The molecular structure is 6-alpha, 9-difluoro-11-beta-hydroxy-16-alpha-methyl-21-valeryloxy-1,4-pregnadiene-3,20-dione.[72]
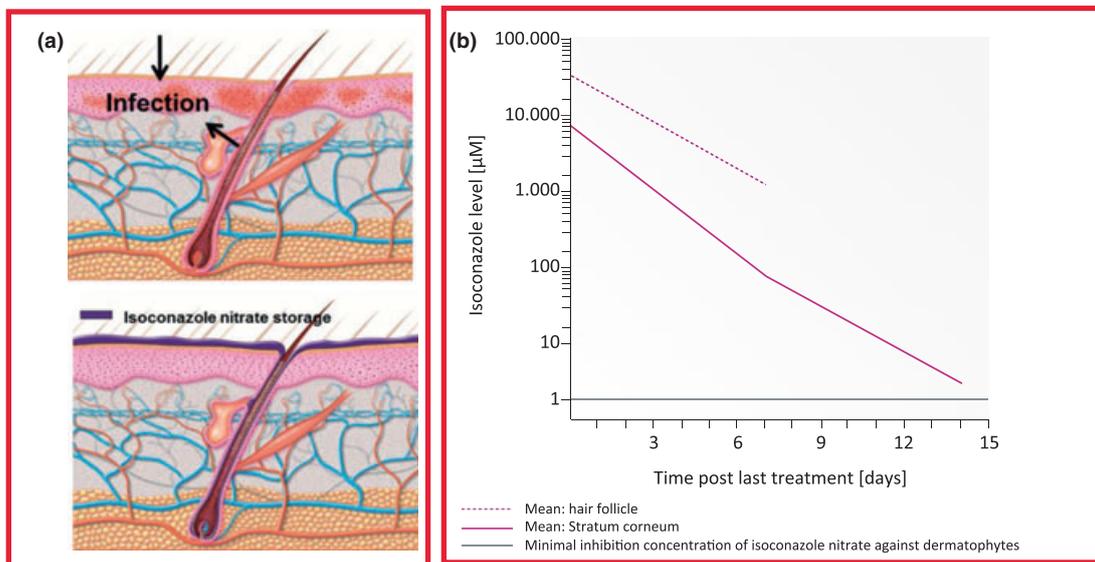

Figure 4 Isoconazole nitrate concentration in the stratum corneum and hair follicle. Isoconazole nitrate in the hair follicle (a) and stratum corneum (a, b) up to 2 weeks after the last application of Travocort on the forearm of nine evaluable volunteers.[25] (MIC for growth inhibition of bacteria and fungi.[8])

From a pharmacokinetic standpoint, the combination of ISN with a topical corticosteroid, such as DFV, can confer unique benefits, such as enhancement of the antimicrobial effects of ISN. In animal models, the addition of DFV to the ISN preparation resulted in two- to threefold higher cutaneous concentrations of ISN in the dermis and epidermis. The increased bioavailability of ISN in combination with a topical corticosteroid is thought to be due to the vasoconstrictive activity of the topical corticosteroid, which delays the circulation-based dispersal of ISN.[26] After 24 h of exposure to ISN in combination with DFV, the concentrations of ISN in the epidermis and dermis reached 120 and 13 μg ml^{-1}, respectively, compared with 40 and 4 μg ml^{-1} for ISN alone.[24] Compared with antimycotic therapy alone, this combination can prolong the duration of antimycotic activity, which is likely to result in faster clearance of fungal infections.[69,70]

When combined, ISN does not influence the penetration and percutaneous absorption of DFV. Like ISN, DFV also penetrates rapidly into the skin, leading to SC concentrations of approximately 150 μg ml^{-1} (300 μmol l^{-1}) after 1 h.[61] These levels are maintained for at least 7 h following initial exposure. DFV levels in the deeper epidermis were about 0.15 μg ml^{-1} (0.3 μmol l^{-1}). However, the percutaneous absorption of DFV is low. Upon entering the systemic circulation, DFV is hydrolysed to diflucortolone and the corresponding fatty acid within minutes. Following intravenous injection, diflucortolone and its metabolites are eliminated from the plasma with a half-life of 4–5 h and ~9 h, respectively, and are excreted in a ratio of 75 : 25 with urine and faeces.[61]

Clinical efficacy of a combination therapy: Travocort
Travocort cream contains both 1% ISN and 0.1% DFV,[61] which delivers higher potency anti-inflammatory action compared with the class I/II corticosteroids found in most other combination therapies.[73] DFV suppresses inflammation and has been shown to alleviate itching, burning sensation and pain.[74] Travocort is indicated for superficial dermatomycoses accompanied by inflammatory skin signs and symptoms where involvement of gram-positive bacteria might be suspected.[61]

The complementary efficacy of this combination has been demonstrated in several controlled randomised studies, and most significantly, in patients with markedly inflammatory mycoses.[44,75–77] Within only 1 week of treatment, the combination clearly showed better results in a double-blind, two-week clinical study ($N = 30$) comparing Travocort with Travogen (1% ISN) for the treatment of severe inflammatory dermatomycoses caused by *C. albicans, T. rubrum, T. mentagrophytes* and *E. floccosum*. A faster reduction in itching (69%), scaling (66%) and erythema (69%) with Travocort vs. Travogen was observed. On average, itching was cured after 2.1 (Travocort) and 3.5 (Travogen) days, erythema after 8.7 (Travocort) and 10.5 (Travogen) days, scaling after 9.1 (Travocort) and 11.2 (Travogen) days. Furthermore, the mycological cure rate after the second week was higher with Travocort (97%) than with Travogen (90%).[75] In another study ($N = 294$), two-week Travocort treatment followed by two-week Travogen treatment in patients with inflammatory dermatomycoses (caused by *E. floccosum, T. mentagrophytes, T. rubrum* and *C. albicans*) led to very good therapeutic results after only 1 week.[76] Complete remission and negative culture and KOH mount were achieved in 41% of patients after 1 week and in 68% after 2 weeks of combination treatment. In randomised double-blind clinical trials, Travocort treatment produced significantly greater therapeutic results (both in symptoms and in negative cultures) after 1 week, compared with ISN monotherapy.[76] In a more recent study ($N = 58$), both pruritus and erythema resolved more quickly and in a larger percentage of patients with tinea inguinalis after treatment with Travocort compared with ISN alone (Fig. 5).[74]

Safety and tolerability of Travocort

Diflucortolone valerate has a proven safety profile, with a relatively low atrophogenic potential compared with other topical corticosteroids (Fig. 6). In a study with 20 volunteers, DFV had low potential to induce telangiectasia and skin atrophy compared with several other corticosteroids (i.e. 0.1% betamethasone-17-valerate, 0.05% betamethasone-17-21-dipropionate, 0.025% fluocinolone acetonide, 0.1% triamcinolone aceponate, 0.1% halciononide and 0.05% clobetasone-17-valerate).[78] In addition, DFV does not alter skin barrier function up to 3 weeks following a 2-week treatment with Travocort cream, as shown by unperturbed mean transepidermal water loss (TEWL) values over the course of 5 weeks (Fig. 7).[25] All TEWL values were within the range of normal barrier function, meaning that the corticosteroid component of the drug applied did not induce any impairment of barrier function.

From a tolerability standpoint, it is important to consider that the addition of a topical corticosteroid
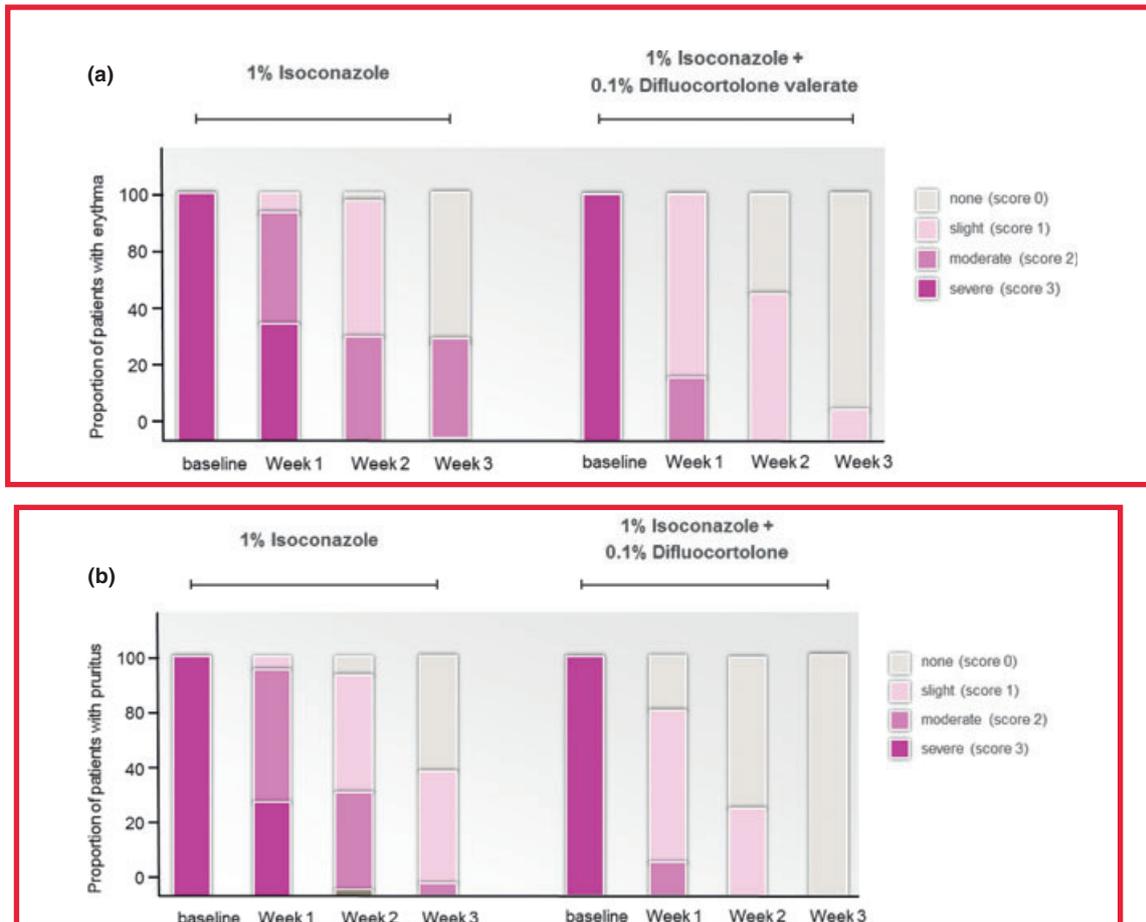
Figure 5 Erythema (a) and pruritus (b) scores at visits 0 to 3 by treatment group. Data from a multicentre retrospective study comparing the mycological and clinical efficacy and tolerability of isoconazole nitrate vs. isoconazole nitrate and diflucortolone valerate in 58 adult patients with tinea inguinalis. Erythema and pruritus resolved more rapidly in the combination group, with evidence of the advantage of combination therapy during the whole study period.[74]

can also mitigate the skin reactions that occur during standard antimycotic therapy. That is, the effects of the topical corticosteroid can offset the sensitivity reactions to the active (or other) ingredients and symptoms of the overtreatment phenomenon, which is caused by the release of fungal toxins.[69]

Data from 40 years of clinical experience and numerous clinical trials demonstrate that Travocort is remarkably safe and well tolerated. After 20 years of postmarketing surveillance (Periodic Safety Update Reports) and a vast treatment experience (>100 million patients treated), it can be concluded that Travocort has never been rejected for safety reasons by an authority and was never withdrawn from any market due to safety reasons. Moreover, only 19 medically confirmed adverse drug reaction case reports were recorded for Travocort in the Global Pharmacovigilance Database (Data on file).

Discussion

Superficial fungal skin infections, or dermatomycoses, are associated with a broad range of pathogens, including dermatophytes, yeasts and moulds. Inflammation plays an important role in dermatomycoses because of exo-enzymes such as keratinase produced by the fungal pathogen at the site of infection. Inflammatory symptoms and signs, such as pruritus and erythema, are highly prevalent in dermatomycoses and are frequently associated with reduced skin-related quality of life.[70,79] Involvement of gram-positive bacteria is also often suspected in this condition. The imidazole ISN is a broad-spectrum antimicrobial agent with a highly effective antimycotic and gram-positive antibacterial activity, a rapid rate of absorption and low systemic exposure potential.[8,21,22,24–26,43,44,69,74–77,80] ISN is effective against dermatophytes, yeasts, yeast-like fungi
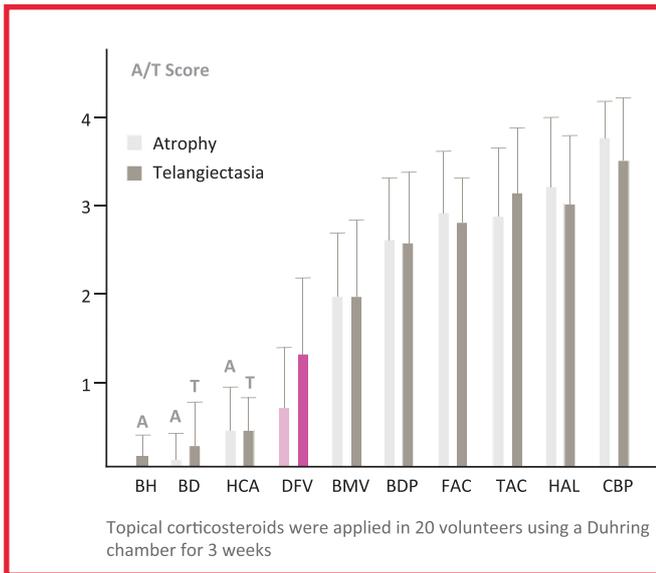
Figure 6 Mean atrophy (A) and telangiectasia (T) scores after 3 weeks of occlusive treatment with various clinically relevant corticosteroid creams.[78] BD: base for DFV; BDP: betamethasone 17-21-dipropionae 0.05% oil/water cream; BH: base for hydrocortisone; BMV: betamethasone 17-valerate 0.1% oil/water cream; CBP: clobetasol 17-propionate 0.05% oil/water cream; DFV: diflucortolone valerate 0.1% water/oil cream; FAC: fluocinolone acetonide 0.025% and 0.2% oil/water cream; FAPG: halcinonide 0.1% fatty alcohol-propylene glycol ointment; FLU: fluocinonide 0.05% FAPG ointment; HCA: hydrocortisone acetate 1.0% in DFV water/oil cream base; HCB: hydrocortisone 17-butyrate 0.1% oil/water cream; TAC: triamcinolone acetonide 0.1% and 0.5% oil/water cream.
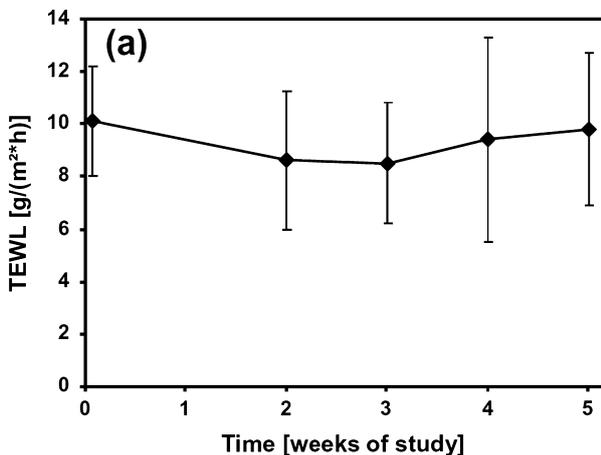

Figure 7 Time course of mean transepidermal water loss (TEWL) of the skin up to 3 weeks after the end of two-week treatment with Travocort cream on the forearm of nine evaluable volunteers. All TEWL values were within the range of normal barrier function.[25]

(including the causative organism of pityriasis versicolor), moulds and *C. minutissimum*, with MICs that are considerably below the concentration of ISN in the skin

and hair follicles following application. Of clinical importance is the finding that hair follicles can also function as long-term reservoirs for ISN, thereby providing a long-lasting therapeutic effect and potentially preventing re-infection.

The combination of ISN with the safe and potent class III corticosteroid DFV (Travocort) provides patients who have dermatomycoses with a triple-action topical treatment—one that also addresses the inflammatory aspect of the disease. Compared with ISN monotherapy, Travocort has a faster onset of antimycotic action, faster relief of itch and other inflammatory symptoms, improved overall therapeutic benefits and improved mycological cure rate. The rapid alleviation of itch results in less damage to the skin barrier due to scratching, and therefore, reduces the chance of secondary bacterial infections. In addition to improving inflammatory symptoms, the combination with the corticosteroid increases the local bioavailability of ISN and prolongs its activity, leading to more rapid normalisation of skin conditions. Travocort is not only effective in the treatment of inflammation and mycotic infections but also in the eradication of accompanying bacterial infections caused by gram-positive bacteria. Travocort does not contain an antibiotic agent, and therefore, does not contribute to antibiotic resistance. From a treatment standpoint, a potent corticosteroid in combination with effective antimicrobial therapy facilitates a rapid visible improvement in superficial mycoses. Because of this and its remarkable safety and tolerability profile, treatment with Travocort results in greater patient satisfaction, and may be an effective tool to increase treatment adherence in patients with dermatomycoses (accompanied by inflammatory signs and symptoms), without compromising safety.

Acknowledgments

Conflicts of interest

Stefano Veraldi is a consultant for Intendis GmbH.

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