Title
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Review

Why rifampin (rifampicin) is a key component in the antibiotic treatment of hidradenitis suppurativa: a review of rifampin's effects on bacteria, bacterial biofilms, and the human immune system

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Abstract

Combinations of rifampin and clindamycin or rifampin, metronidazole, and moxifloxcin have been reported as effective treatments for hidradenitis suppurativa (HS) Hurley Stage 1 and Hurley Stage 2. Clinical trials suggest that for stage 1 and mild stage 2 HS, clindamycin 300 mg twice daily and rifampin 300 mg twice daily for 10 weeks can substantially abate HS in ~80% of cases and remit HS in ~50% of cases. Another study notes use of rifampin-moxifloxacin-metronidazole given for 6 weeks, dosed as rifampin (10 mg/kg once daily), moxifloxacin (400 mg daily), and metronidazole (500 mg thrice daily) with the metronidazole stopped at week 6. Rifampin and moxifloxacin were continued if the HS improved and side effects did not occur. Using this triple antibiotic regimen remission occurred in 100% Hurley Stage 1, 80% Hurly Stage 2, and 16.7 % of Hurley Stage 3 HS. The author typically gives HS clindamycin 300 mg and rifampin 300 mg, each twice daily, for 10 weeks and assesses if remission has occurred. If the patient has not achieved remission the author continues the regimen as long as the patient's clinical status continues to improve without side effects. The reasons why rifampin is so effective against HS have not been fully defined and might involve rifampin's (1) antibacterial effects (2) effects on bacterial biofilms (3) anti-inflammatory effects (4) effects against granulomas (5) and immunomodulatory effects on neutrophils. It is notable that rifampin, although not first line, is an effective treatment for *Clostridium difficile*, a pathogen that arises during treatment with clindamycin. Thus, rifampin enhances safety when rifampin and clindamycin are combined for the treatment of HS.

Introduction

Rifampin (name in United States) and rifampicin (name used outside United States) is an antibiotic with varied biochemical effects that inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase [1]. Crystal structure data and biochemical data indicate that rifampin binds to RNA polymerase at a site adjacent to the RNA polymerase active center and blocks RNA synthesis by physically blocking the formation of the phosphodiester bond in the RNA backbone, preventing extension of RNA products beyond a length of 2–3 nucleotides ("steric-occlusion" mechanism) [2].

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a complex inflammatory disease that centers on a dysfunctional human follicular unit. The etiology of HS remains to be fully defined but appears to involve an aberrant cutaneous immune response to commensal bacteria,

in particular, coagulase negative staphylococci (CONS) and bacterial biofilms. Although HS usually occurs in intertriginous areas, HS can affect any area of the body with hair follicles. Clinically, HS manifests as pustules, abscesses, comedones, cysts, and pyogenic granulomas that evolve into scars, keloids, fibrosis, granulomas, sinus tracts, and fistulas (Figure 1, 2, 3, 4).

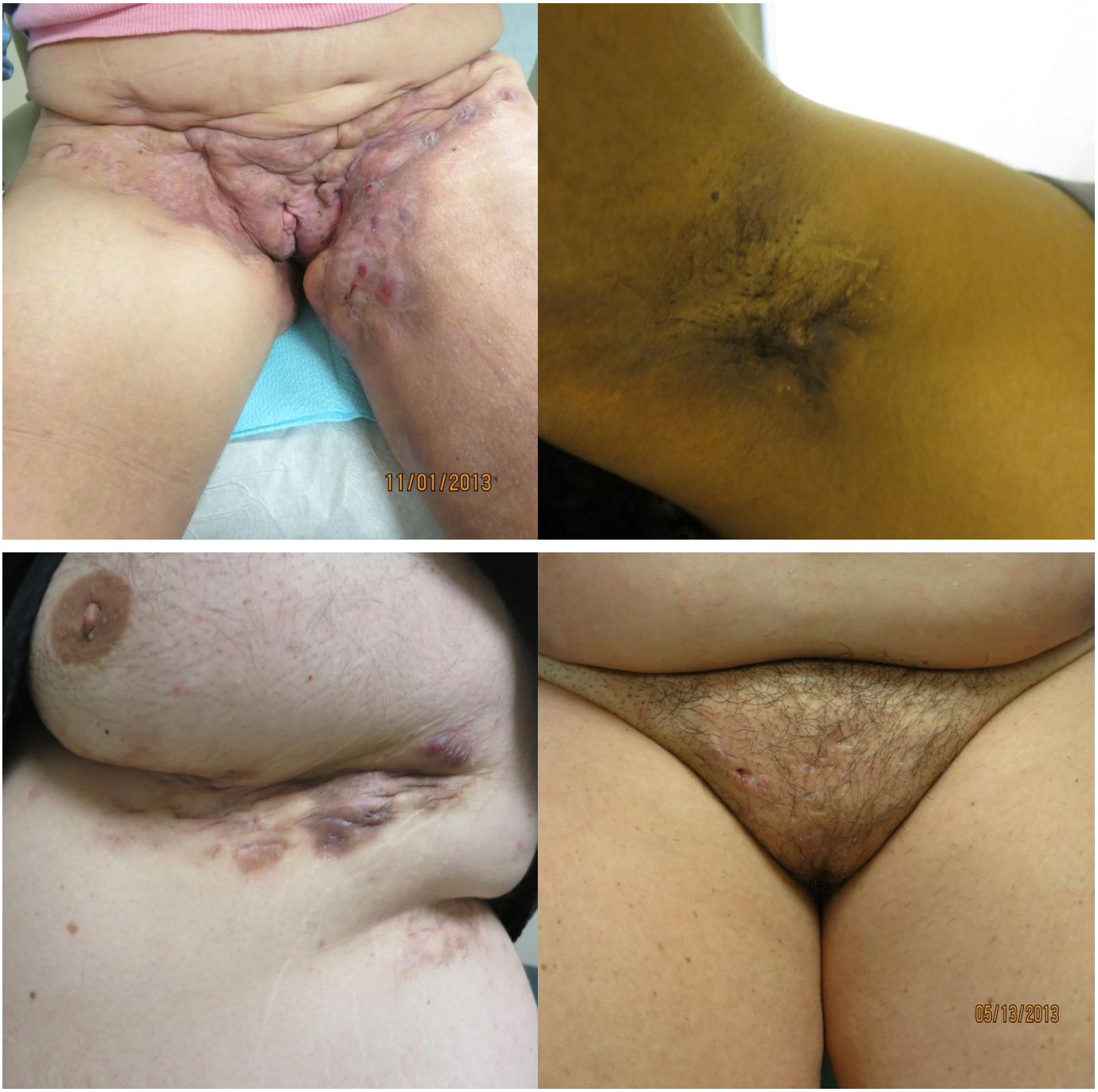

Figure 1. Stage 3 Hidradenitis involves extensive keloidal scarring of the inner thighs groin with pyogenic granulomas manifest on the left leg. Note the left side has more extensive disease than the right side. **Figure 2**. Stage 2 Hidradenitis of the axilla with keloidal scarring and acne inversa lesions **Figure 3**. Stage 2 Hidradenitis manifesting as scars and keloids under the breast of an obese man. Note that there are active abscesses on the far left of the picture. **Figure 4**. Stage 1 Hidradenitis manifested as an isolated sinus tract with one ostia

The inflammatory infiltrate contains lymphocytes and neutrophils, but not eosinophils; sometimes bacteria are contained inside the follicle itself. The histology has been described (Table 1) (Figure 5, 6,7,8) (Images courtesy of Joan Mones DO FABP Ackerman Academy of Dermatopathlogy [3].

Table 1.

Poral occlusion,	Bacteria in base of follicle	Sinus tracts	Epithelial cyst	Abscess(es)	Diffuse dermal inflammation	Sinus tract

Apocrine glands	Eccrine glands	Neurophilic infiltrate	Apocrine glands	Lymphocystic infiltrate	Granulomas	

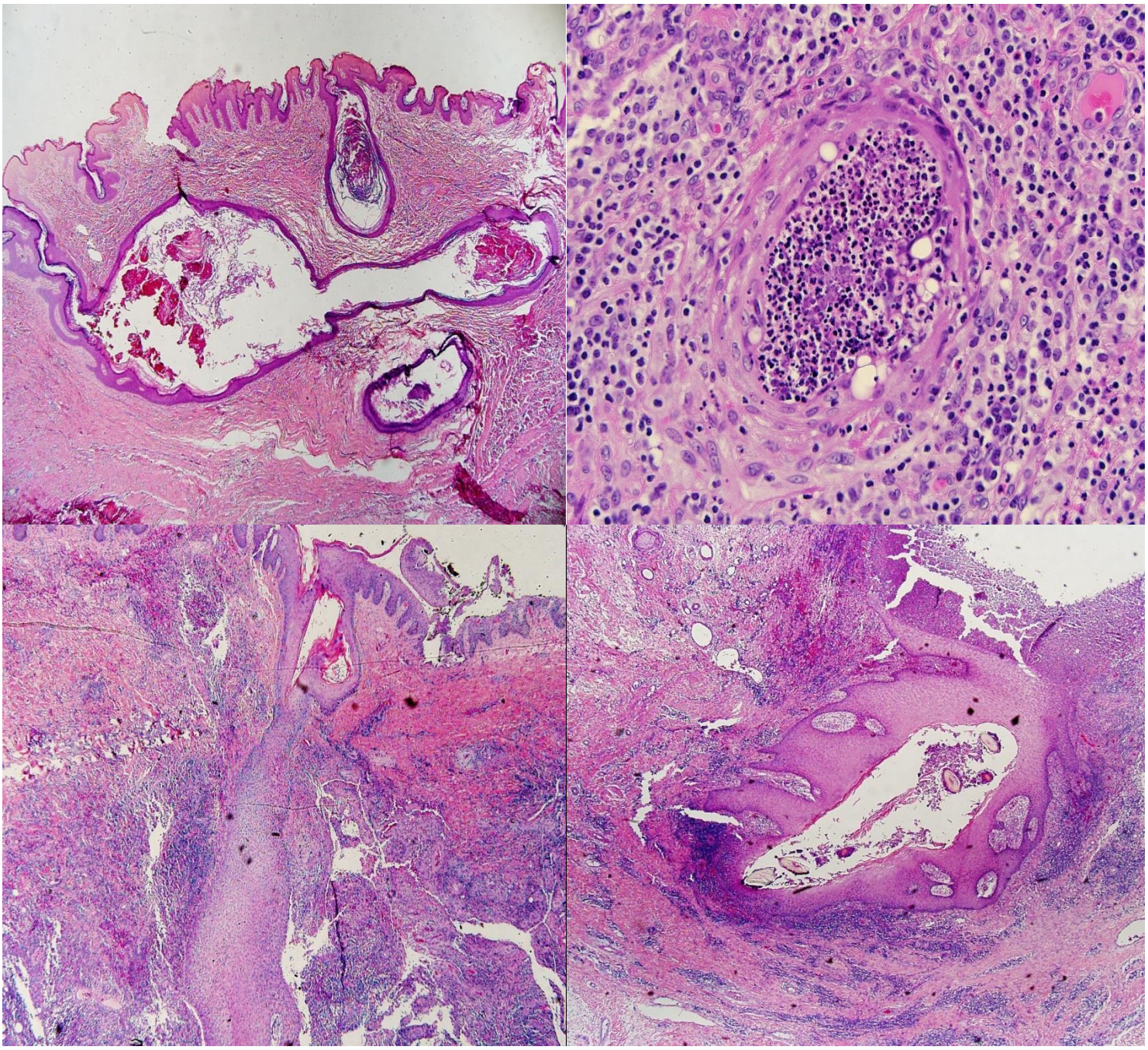

Figure 5. Multiple large squamous epithelial lined cysts are present in the dermis. The cysts emanate from the infundibular epithelium of the epidermis. Note the absence of significant inflammation. (Hematoxylin & eosin stain; 20x magnification). **Figure 6.** Abscess with surrounding fibrosis and acute and chronic inflammation. (Hematoxylin & eosin stain; 200x magnification). **Figure 7.** Extensive inflammation in the dermis surrounding portion of a large epithelial cyst. (Hematoxylin & eosin stain; 100x magnification). **Figure 8**. Cystic dilatation of entrapped squamous epithelium in dermis. There is rupture of the lower portion of the cyst with associated suppurative inflammation. Fragmented hair shafts with inflammatory exudate are present with in the upper portion of the cyst (Hematoxylin & eosin stain; 40x magnification).

Rifampin is pivotal part of antibiotic treatment of HS

Rifampin combined with clindamycin should be the first line antibiotic treatment for HS. Clinical trials suggest that for stage 1 and mild stage 2 HS, clindamycin 300 mg twice daily and rifampin 300 mg twice daily for 10 weeks can substantially abate HS in ~80% of cases and remit HS in ~50% of cases [4,5,6]. Another study notes use of rifampin-moxifloxacin-metronidazole given for 6 weeks dosed as rifampin (10 mg/kg once daily), moxifloxacin (400 mg daily), and metronidazole (500 mg thrice daily) with the metronidazole stopped at week 6 [7]. Rifampin and moxifloxacin were continued if the HS improved and side effects did not occur. Using this triple antibiotic regimen remission occurred in 100% Hurley Stage 1 80%, Hurly Stage 2, and 16.7 % of Hurley Stage 3 HS

The author sometimes uses the combination of rifampin 300mg twice daily and minocycline 100 mg twice daily or extended release minocycline extended release 115 mg if response to clindamycin and rifampin 300mg, each twice daily, is not adequate. Sometimes the author adds amoxicillin and clavulanate potassium to a rifampin/clindamycin or rifampin/minocycline combination regimen if (1) bacteria are cultured out of abscesses (e.g. klebsiella pneumoniae) are sensitive to amoxicillin and clavulanate potassium or (2) the patient is not responding sufficiently to the rifampin bimodal combination treatments, as some evidence suggests amoxicillin and clavulanate potassium is highly active against the bacteria that cause HS [8]. The amoxicillin and clavulanate potassium is continued until the HS abscess pus is culture negative or the patient improves if culture data is not relevant to treatment. The author also uses combinations of rifampin 300mg twice daily with levofloxacin 500 mg daily for 2-4 weeks if culture data suggests that levofloxacin would cover bacteria growing out for HS lesions and then resumes combination treatment with rifampin and clindamycin or rifampin and minocycline or minocycline extended release. If the patient has not achieved remission, the author continues the regimen as long as the patient's clinical status continues to improve without side effects. Rifampin and clindamycin are not used with pulse dosing. However, if the patient achieves remission at 10 weeks and then relapses later, another 10 weeks of rifampin and clindamycin or continuous use of rifampin and clindamycin can be considered.

The reasons why rifampin is so effective against HS have not been defined. Reasons for rifampin's efficacy might involve (1) antibacterial effects (2) effects on bacterial biofilms (3) anti-inflammatory effects (4) effects against granulomas and (5) immunomodulatory effects on neutrophils. It is notable that rifampin is an effective albeit second line treatment for *Clostridium difficile*, a pathogen that arises during treatment with clindamycin making the combination of rifampin and clindamycin a safe and effective treatment for HS.

Staphylococcus aureus, Streptococcus pyogenes and other Streptococci

Staphylococcus aureus, *Streptococcus pyogenes* (group A) and other *Streptococci* (Group B and group C) can be cultured from the abscesses of HS but their significance is unclear. Interestingly, the author has found some patients who clinically respond to rifampin and clindamycin, but who consistently culture group B and group C streptococci despite months of treatment with rifampin and other antibiotics including amoxicillin and clavulanate potassium. Is likely that antibiotics such as amoxicillin and clavulanate potassium do not clear the streptococci from the lesional skin of HS owing to the biofilm effect. The streptococci cultured out of HS lesions are sensitive to these antibiotics The biofilm effect might also account for chronic carriage of *Staphylococcus aureus* in the nose (20-25%) of United States population, for chronic pharyngeal carriage of *Streptococcus pyogenes*, and rectal and anal colonization by Group B *Streptococci*.

Coagulase negative staphylococcus

There are dozens of species of coagulase-negative staphylococci (CONS), which inhabit human skin. CONS, including *Staphylococcus epidermidis* (SE), a coagulase-negative species, are commensal skin bacteria. SE is the most frequently recovered staphylococcal species [9]. SE colonizes the body surface and it is particularly prevalent on moist areas such as the axillae, inguinal area, perineum, anterior nares, conjunctiva, and toe webs. There are dozens of subspecies of SE [10]. SE can cause severe infections in immuno-suppressed patients and those with central venous catheters [11,12].

Other species of CONS exist. S. saprophyticus, another coagulase-negative species that is part of the normal vaginal flora, is predominantly implicated in genitourinary tract infections in sexually active young women. The CONS bacterium *S. haemolyticus* and *S. hominis* are preferentially isolated from axillae and pubic areas high in apocrine glands. *S. lugdunensis* primarily colonizes the lower extremities and inguino-perineal area, the later being a common site of HS [13]. *S. capitis* is found surrounding the sebaceous glands on the forehead and scalp following puberty. *S. auricularis* is part of the human external ear microbiota, exclusively colonizing this region. *S. schleiferi* and *S. caprae* also preferentially live on moist human tissue. In recent years, *Staphylococcus species* have been implicated in orthopedic implant infections, biofilm related infections, and wound infections. Factors such as the particular species of CONS that stimulates the immune system of an HS patient and the exact body site habitat of that CONS might define the clinical areas (e.g. axillae, groin, breasts, ears) effected in an individual HS patient. The existence and distribution of SE and other CONS can explain why HS favors intertrigious areas; one study noted that bacteria were recovered in 49% of all HS lesions and that 40% of bacteria recovered were Staphylococcus epidermidis [14].

In another study of 82 patients with 102 HS lesions in France, *S. lugdunensis* was present in 58% of HS nodules and abscesses [15]. Rifampin is effective in combination with other antibiotics against *S lugdunensis* [16]. Notably, deep tissue samples of HS have always demonstrated (CONS) [17].

Milleri group streptococci and Corynebacterium

Streptococcus milleri has been implicated as an aggravating factor of perineal HS [18]. Rifampin in combination with other antibiotics has good activity against the Milleri group of streptococci, which are commensal oropharyngeal, gut, and genital tract florae. These include: *Streptococcus milleri*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius* [19]. This group of bacteria has been implicated as a cause of HS [20]. C*orynebacterium species* in deep tissue samples have been demonstrated in HS [21]. Most strains of *Corynebacterium diphtheriae* are susceptible to rifampin [22].

Effect of rifampin on biofilms

The term, biofilm, describes any group of microorganisms in which these cells (1) stick to each other and (2) often adhere to a surface. Although HS is not caused by the intrinsic pathological effects of the bacteria, HS is an inflammatory disease related to the stimulation of the immune system by bacteria and their biofilms [23,24]. Rifampin is effective alone or in combination with other antibiotics against some, but not all, of the bacteria that make up biofilms and mitigate the biofilms themselves [25,26]. *Staphylococcus epidermidis* biofilms often can be controlled with the use of a combination of N-acetylcysteine and rifampicin [27]. Research confirms that rifampicin at a concentration of 1.2 mg/mL immediately reduces established biofilms formed by *S. epidermidis* although it is not bactericidal despite very low MICs at planktonic conditions [28]. In another experiment, rifampin penetrated biofilms formed by *S. epidermidis*, but failed to effectively kill the bacteria [29]. Tests on the bacteria and their biofilms have shown that *Propionibacterium acnes* bacteria and their biofilms can play a pathogenic role in HS. In a study of archival samples from 27 patients with HS, *P. acnes* was found in biofilms in hair follicles of two patients [30].

Rifampin used as a treatment for inflammatory skin disease-psoriasis

It appears that rifampicin can sometimes cause immunosuppression in conventional doses in psoriasis patients by suppressing T-cell function [31]. This might contribute to its efficacy against HS, but this effect needs further definition. Rifampin has been used as a treatment for psoriasis vulgaris [32,33] and guttate psoriasis [34]. The role of rifampin's anti-streptococcal effects as the basis for its effect on psoriasis is controversial. One report [35] related rifampin's effect on psoriasis to anti-streptococcal effects. The addition of 5 days of rifampin to a 10- or 14-day course of penicillin or erythromycin greatly reduced the rate of chronic streptococcal carriage. Furthermore, the empiric use of rifampin in combination with penicillin or erythromycin in nine patients with streptococcal-associated psoriasis coincided with abatement of their psoriasis. Besides cases reports, there is no evidence from clinical studies that anti-streptococcal interventions for guttate and chronic plaque psoriasis are effective [36].

Rifampin used as a treatment for inflammatory skin disease-of the hair follicle

Rifampin can abate inflammatory skin diseases that involve the hair follicle. Rifampin and clindamycin have been used for effective treatment of HS, dissecting cellulitis [37], folliculitis decalvans [38], and tufted folliculitis [39,40]. Dissecting cellulitis of the scalp has been effectively treated with rifampicin and isotretinoin [41].

Rifampin as a treatment for inflammatory skin disease-granulomatous

Granuloma annulare (GA) has been noted to respond to antibiotic combinations using rifampin. There is one report of 6 cases of GA [42], resistant to the standard modalities of treatment that resolved after 3 months with monthly rifampin (600 mg), ofloxacin (400 mg), and minocycline hydrochloride (100 mg). These 6 patients received 4-8 pulses of once monthly rifampicin, ofloxacin, and minocycline until all skin lesions cleared completely [43]. An open-label, prospective study of 21 patients with GA who received once monthly rifampin, ofloxacin, and minocycline for 6 months showed this regimen to be partly effective in 71% of patients and ineffective in 29% of patients [44].

The response of GA to rifampin-based combinations has implications for HS, which is sometimes a granulomatous disease [45,46]. Rifampin might help break down the granulomas of HS and aid in the treatment of HS via this anti-granuloma effect. One study of HS of 101 patients, noted epithelioid granulomas in 8% of cases and foreign body type granulomas adjacent to ruptured hair follicles, sinus tracts, or nearby degenerate sweat glands in 25% of cases [47].

Rifampin has anti-inflammatory effects on human polymorphonuclear lymphocytes

Rifampin has anti-inflammatory effects on immunomodulatory gene expression and cellular function in human inflammatory cells (neutrophils, eosinophils, and basophils) [48]. As the immune response of HS involves the aberrant effect of neutrophils, the down regulation of neutrophil activity by rifampin might abate HS.

Clostridium difficile colitis

Clostridium difficile colitis (CD) or pseudomembranous colitis is inflammation of the large intestine resulting from infection with CD. Although not a first line treatment for CD, rifampin is an effective second line treatment for CD [49]. In one study of 180 isolates of pathogenic CD from Canada and Italy, only 10% were resistant to rifampin [50]. The author has seen only 2 case of CD develop in over 800 patients treated with clindamycin and rifampin.

Conclusion

HS remains an enigmatic disease without a cure. However, the importance of bacteria as a stimulus for HS seems certain. The basis for the utility of rifampin for the treatment is not mysterious. Rifampin's varied suppressive effects on bacteria and on the immune system itself make it a most useful treatment. The combination of rifampin and clindamycin against HS is single best initial antibiotic treatment for HS [50, 51]. Rifampin's activity against *Clostridium difficile* makes it an even more useful agent when used in combination with other antibiotics. As more treatments emerge for HS, the combination of new agents with rifampin and other antibiotics will likely enhance the response of HS patients to treatment.

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