

IN-DEPTH REVIEW

Combination Treatment for Hidradenitis Suppurativa

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ABSTRACT

Background: The treatment of hidradenitis suppurativa remains challenging, despite recent advances. A diverse range of management options, from lifestyle measures to monoclonal antibodies, are available and utilized based on disease severity and other patient factors. Increasingly, it is thought that combination therapy may be more adept in meeting the challenges of treatment of this multimodal disorder.

Methods: A literature review of existing studies was performed. Eligible studies for the present review included case reports, case series, cohort studies or clinical trials in which patients with hidradenitis suppurativa were treated with a combination of two or more medical treatments. Abstracts, conference presentations, editorials, reviews, and expert opinions were excluded from analysis.

Results: A total of 23 studies were identified from systematic database searches after applying inclusion and exclusion criteria. The majority of treatments documented are systemic antibiotic combinations, however a minority relate to topical and biological agents. The treatment combinations had varying degrees of efficacy.

Conclusion: There is evidence that combination therapy is effective in the treatment of hidradenitis suppurativa. However, the data is limited, and further, more robust, prospective studies with larger cohorts are required to reaffirm the findings in the present review.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, debilitating inflammatory cutaneous disorder, characterized by recurrent abscesses, nodules, sinus tracts, fistulas and scarring in apocrine bearing skin. The reported prevalence of HS ranges from 0.03-4%, with variability depending on geographical location.¹

The exact mechanism for pathogenesis of HS is unknown, but thought to be a combination of genetic, and environmental factors^{2,3} with resultant immune dysregulation, follicular occlusion inflammation and secondary infection and tissue destruction.⁴

The treatment of hidradenitis remains challenging, despite recent advances. A diverse range of management options, from lifestyle measures to monoclonal antibodies, are available and utilized based on disease

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severity and other patient factors.^{5,6} Increasingly it is thought that combination therapy may be more adept in meeting the challenges of treatment of this multimodal disorder.

We aim to provide a comprehensive review of the of the combination therapies used in the treatment of HS.

METHODS

Electronic searches were performed using Ovid Medline, Cochrane Central Register of Controlled Trials, PubMed, ACP Journal Club, Cochrane Database of Systemic Reviews (CDSR), and the Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to May 2023. We combined the terms: combination, treatment, therapy and hidradenitis suppurativa as key words of MeSH headings in order to maximize the search strategy. Reference lists of all retrieved articles were also assessed for any relevant articles using the exclusion and inclusion criteria.

Eligible studies for the present review included case reports, case series, cohort studies or clinical trials in which patients with hidradenitis suppurativa were treated with a combination treatment. Combination was defined as two or more systemic, medical treatments. Procedural and surgical treatments were excluded. Language was restricted to English and only human subjects were included.

RESULTS

Nineteen articles met the search criteria and are presented in the **Table 1**.

Clindamycin and Rifampicin

The most common antibiotic combination therapy in the literature for HS is oral clindamycin and rifampicin. The outcomes of combination clindamycin and rifampicin (CCR) for the treatment of HS have been reported in 12 studies to date, consisting of 440 patients.⁷⁻¹⁸ The usual treatment regime was typically 600mg clindamycin and 600mg rifampicin daily, with variations in dosage/treatment schedule.

There is significant heterogeneity in reported outcomes. Most studies reported clinical outcomes including Hurley score, Sartorius score, complete remission, and hidradenitis suppurativa clinical response (HiSCR). Some studies, included psychological outcome measures such as the Dermatology Life Quality Index (DLQI) and Skindex questionnaire.

The primary outcomes varied across the studies. Complete remission was reported in 3 studies and ranged from 1-57%.^{9,11,14} However, partial remission was only reported by van der Zee et al. and observed in 35% of patients.¹⁴ In 3 studies, the primary clinical outcome was the HiSCR, defined as at least, a 50% reduction in inflammatory lesion count and no increase in abscesses or draining fistulas. Dessinoiti et al used a similar, novel clinical response score, defined as at least 50% clinical improvement from baseline. The proportion of patients achieving these measures was a range of 33-57% and 73% respectively.^{10,12,13,15} Four studies reported Sartorius score or the modified Sartorius score as a primary outcome measure, with mean reductions of 16%-68.5% and a median reduction of 50% amongst the studies.^{7,10,11,17} Yao et al. reported the Hidradenitis Suppurativa Score (HSS) as their primary endpoint and demonstrated a

12 point improvement in median score with therapy.¹⁶

In terms of side effects across the pooled cohort, a total of 17% reported diarrhea, and 10% other gastrointestinal symptoms including nausea, vomiting, abdominal pain and digestive discomfort. There were only two patients experiencing candida vaginitis across the literature.

Rates of relapse after cessation of treatment was reported in only 4 of the studies.^{9,12,13,15} Mendoca et al reported no relapse in 8/14 (57%) patients that responded to treatment. Dessinoiti et al had 10/26 (38%) patients relapse after a mean of 4.2 months whereas Caro et al. reported 15/30 (50%) patients with relapse after a mean of 12.4 weeks and 68% of patients after a mean of 24.9 weeks in two separate studies.

Rifampicin-moxifloxacin-metronidazole

We found 2 studies investigating the efficacy of a combination of rifampicin-moxifloxacin-metronidazole (RMoM).^{19,20} In a retrospective review by Join-Lambert et al. of 28 patients treated with a 3-week course of IV ceftriaxone and oral metronidazole as induction therapy before RMoM, clinical remission was observed in 16 people.¹⁹ However, only 2 of these patients had severe, Hurley stage 3 disease. Gastrointestinal side effects including nausea and diarrhea occurred in 64% of patients. Vaginal candidiasis and moxifloxacin tendinitis were seen in 25% and 14% of patients, respectively.

In the same study site, Delage et al. conducted a prospective study of 28 patients in 2020, and clinical remission was seen in 21 patients.²⁰ Adverse events including mild digestive discomfort, mucosal candidiasis, and asthenia was observed in 96%, 64% and

79% of patients, respectively. The treatment protocol between both studies also varied as the latter substituted pristinamycin, cotrimoxazole or doxycycline in the case of adverse drug reactions.

Combinations with at least one antibiotic

Several other combination treatments that included an antibiotic were found in our literature search. Armyra et al. conducted a prospective study of 20 patients with HS treated with a combination minocycline and colchicine for 6 months, followed by a maintenance regimen of 0.5mg oral colchicine twice per day for 3 months.²¹ Clinical improvement was observed in all patients and only 15% of patients experienced nausea and diarrhea after 9 months of treatment.

Delaunay et al. conducted a retrospective audit of 65 patients treated with a combination of clindamycin and ofloxacin.²² A complete response was observed clinically in 34% of patients and a partial response in 25% of patients. Eighteen patients reported secondary adverse events, including 12% with clinical or biological symptoms such as worsening renal function and anemia, and 8% of patients experienced intermittent diarrhea. Eleven of these patients had to cease treatment due to side effects.

Fania et al. completed a prospective study of 37 patients using intralesional ultrasound-guided injections of triamcinolone plus lincomycin, at baseline and after 2 weeks.²³ There was a statistically significant reduction in mean, clinical (12.2 to 6.8), pain VAS (4.6-1.5), and skindex (60.3 to 49.6) scores. There was 1 case each of fever, increased acanthosis nigricans, and a delayed menstrual cycle in 3 different patients. However, 15 patients were on concomitant

therapy including adalimumab, doxycycline, clindamycin, oral acitretin and dapsone.

There has also been a single case report of a patient taking a combination of intravenous linezolid and meropenem for one month with complete remission observed during treatment, however relapse occurred shortly afterwards.

Other Combination treatments

There were 3 retrospective studies which included combination therapies that did not include antibiotics. One study, by Hessam et al., looked at 66 patients treated with a combination of oral zinc gluconate and 2% topical triclosan.²⁴ They reported a mean reduction mHSS score from 32.5-25 and a statistical improvement in clinical and quality of life scores.

Mcphie et al looked 31 patients that had received various combination treatment.²⁵ The best clinical outcomes included CCR for mild disease, spironolactone & dapsone gel for moderate disease, and isotretinoin/adalimumab, adalimumab/tetracycline, isotretinoin/spironolactone, and intralesional steroid/tetracycline for severe HS. However, the case numbers for each modality was very low.¹⁻⁶

Literature regarding combination treatment that include biologics have also been very limited, despite the emerging evidence for its efficacy for HS.²⁶ Brunasso et al. described a small case series of 7 patients with HS treated with a combination of infliximab and methotrexate.²⁷ Data was documented from the two years following treatment (114-122 weeks). Short term results were promising with a mean reduction of pain in 96.2%, quality of life improved in 52%, and a 7% reduction of affected area. However, at the 2-

year follow-up, pain was reduced only by 34.8%, quality of life improvement was in 14.7%, and a 1.25% reduction in the affected area. A single case report of dapsone and infliximab in combination has also been trailed in a patient with HS with significant clinical improvement of lesions.²⁸ Another case series of sirolimus used as a rescue therapy in combination to tumor necrosis factor inhibitors demonstrated improvement in 78% of patients with severe refractory HS.²⁹

DISCUSSION

HS is primarily a chronic inflammatory disease affecting apocrine glands. Several treatment modalities have been recommended for HS including medical and surgical interventions. In mild to moderate HS, topical and systemic antibiotics including clindamycin, rifampicin and tetracycline tend to be the first line treatments.³⁰

The rationale for antibiotic therapy in HS is based on the idea that bacteria is linked to the pathogenesis of the disease. Recent studies investigating the skin microbiome of HS patients with and without lesions, have demonstrated the presence of *Staphylococcus lugdunensis*, polymorphous anaerobic flora and skin commensals, including *Propionimonas* and *Pothoniphilus* species, as the most commonly observed bacteria.^{31,32} Antibiotic combinations in the literature were developed on a basis of their wide coverage for this broad spectrum of bacteria present in HS lesions in addition to prevention of resistance seen with monotherapy and their anti-inflammatory effects.^{33,34}

The use of combination clindamycin and rifampicin is currently used for the treatment of HS and recommended by European

guidelines, due to their broad spectrum antibacterial, immunomodulatory and anti-inflammatory effects.³⁵⁻³⁷ CCR was first trialled in patients with HS on the background of its established effectiveness in patients with other follicular disorder such as folliculitis delcalvans.³⁸ Across all studies investigating the efficacy of CCR in HS, clinical improvement has been observed in reported outcomes measures including complete remission in some patients.^{9,11,14} However, there is a paucity of randomized controlled trials and significant heterogeneity in reported outcomes, making it difficult to combine results. The safety profile is varying with the most commonly reported adverse event being gastrointestinal symptoms, including diarrhea and nausea.

CCR appears to be the most beneficial for patients with mild to moderate disease, and in some of the studies it was observed, that non-responders were typically patients with severe disease.⁷⁻¹⁸ Furthermore, patients using CCR experienced varying relapse rates, demonstrating that this intervention is not curative but feasible for use in symptom relief. Only one study has investigated longer term use of CCR for 6 months demonstrating sustained results during the course of treatment, however, did not include any follow up results after ceasing treatment.¹⁶

Recently it has been demonstrated that rifampicin significantly reduces the clindamycin concentration, and the clinical relevance of this in CCR treatment of HS needs to be elucidated.³⁹ The gastrointestinal side effects of CCR are an important area for future consideration as clindamycin is related to *Clostridium difficile* infection and there has been one report of the infection arising from CCR treatment in HS.^{40,41} Rifampicin monotherapy is linked to antibiotic resistance and recommended for use in association with another antistaphylococcal agent.⁴² Caro et

al. demonstrated that clindamycin monotherapy was slightly more effective than CCR. However, the evidence for this is limited and the risk of antibiotic resistance with clindamycin monotherapy needs to be taken into account.¹²

The combination RMoM was developed in response to issues of antibiotic resistance and diminishing clindamycin concentrations with CCR.²⁰ To provide similar coverage to CCR, the same study site previously identified bacteria including, *Staphylococcus lugdunensis*, polymorphous anaerobic flora and skin commensals from bacterial isolates of their HS patient cohort, before selecting antibiotic agents.^{32,43} The effectiveness of combination therapy of RMoM for HS is comparable to CCR, however RMoM is most suitable for Hurley stage 1 disease. However, there is a relatively high prevalence of adverse events such as mild abdominal discomfort and mucosal candidiasis. Most of these side effects are mild and, in the context of its efficacy, increase its value as an intervention. Unlike CCR, patients treated with RMoM had a relatively lower relapse rate at year follow-up. This may be related to the pharmacokinetics and lesser interaction between rifampicin and moxifloxacin. Rifampicin is an inducer of cytochrome P450 which metabolises clindamycin, diminishing its plasma levels over time.³⁹ Combination ofloxacin and clindamycin is another alternative to CCR and RMoM, sparing rifampicin use for MSSA and MRSA severe infections. This combination demonstrates significant clinical improvement; however, the sample size is extremely low and the prevalence of side effects is relatively high.

Some researchers have investigated the effect of combination therapies which more directly target the inflammatory pathway in HS. Combination minocycline/colchicine and triamcinolone/lincomycin for the treatment of

HS have demonstrated significant reduction in disease with minimal side effects.^{21,23} However both studies are observational in nature, thereby limiting the gravity of the results. Colchicine works primarily via tubulin disruption with the effect of downregulating several inflammatory pathways, making it a potential treatment for HS, due to its overall, anti-inflammatory and immunomodulating effects.⁴⁴ In the study conducted by Armyra et al., investigating a combination therapy of minocycline and colchicine, patients also undertook maintenance treatment with colchicine, which may have affected the results at their 3 month follow up after ceasing combination treatment.

Hessam et al. have investigated unique combinations such as zinc gluconate with topical triclosan demonstrating some clinical and quality of life improvement, however further studies are required to provide stronger evidence for its efficacy.²⁴ Zinc's effect on HS is related to its anti-inflammatory properties and the intimate link to the immune system, similar to its already established use in acne patients.⁴⁵ In combination with the involvement in the antibacterial properties of triclosan, the use of zinc gluconate presents as an alternate therapy for HS.

Biologics have an important role in many inflammatory diseases due to their immunosuppressive properties and are fast emerging as forerunners in the treatment of HS.⁴⁶ Currently, adalimumab is the only food and drug administration (FDA) approved drug for the treatment of HS. Infliximab monotherapy has also been reported in several studies as an effective treatment for HS. However, reports on combination therapy using biologics is extremely limited and reported only in a case report with combination infliximab/dapsone and a small case series using infliximab/methotrexate.^{47,48} In both studies,

the therapy demonstrated significant efficacy. However, the infliximab/methotrexate combination was associated with a poor safety profile and long-term outcomes as many patients relapsed. This is in keeping with previous literature related to infliximab monotherapy for HS which was associated with a high rate of adverse events. The use of biological treatments in combination with other therapies may be useful for severe disease or HS that is unresponsive to other agents and requires further investigation.

LIMITATIONS

The body of literature related to combination treatment in HS is subject to significant limitations. The quantity of studies investigating each intervention is small, with a maximum of 6 for CCR and 1-2 for other interventions. Another limitation is that the outcome studied between reports are all different, which limits comparability. The evidence is also low quality due to being primarily composed of retrospective studies, case series and case reports. Furthermore, the nature of these studies being retrospective or unblinded makes them subject to significant observer bias. Other forms of bias include selection and publication bias, which was significant in the present review as it is likely that only positive results are being published.

CONCLUSION

The current evidence depicts combination therapy as a potentially beneficial treatment modality for HS. However, the current literature is composed mostly, of observational studies and case reports and thus, further research in the form of randomized controlled trials comparing

combination treatment to existing interventions is required.

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Table 1. Characteristics of included studies.

Study	N	Age (Mean)	Treatment Regimen	Reported Outcomes	Effectiveness of Intervention	Adverse Events	Follow Up	Type of study	Level of evidence*
Clindamycin + Rifampicin									
Mendoca, 2006	14	No Characteristics of included studies	Clindamycin 600mg and rifampicin 600mg for 10 weeks	Complete remission (undefined)	8/14 (57%): complete remission	4/14, diarrhea (4)	8 with sustained remission for 1-4 years	Retrospective observational	IV
Van der Zee, 2009	34	40	Clindamycin 600mg and rifampicin 600mg for 10 weeks and other dosages and durations	PGA, partial improvement, defined as <75% from baseline, complete improvement, defined as at least 75% improvement	16/34 (47%): complete remission; 12/34 (35%): partial remission	13/34, diarrhea (9)	NR	Retrospective observational	IV
Gener, 2009	70	33	Clindamycin 600mg and rifampicin 600mg for 10 weeks	Sartorius score, Hurley Skindex-France questionnaire, HS Patient Global assessment	median decrease in Sartorius score from 28 to 14.5; 8/70 (11%): complete remission	10/70, Gastrointestinal (10)	NR	Retrospective observational	IV
Bettoli, 2013	23	38	Clindamycin 600mg and rifampicin 600mg for 10 weeks	Sartorius score; number of exacerbations	17/20 (85%) improved; improvement in mean Sartorius score and number of exacerbations	3/20, nausea and vomiting (3)	NR	Prospective observational	IV
Dessinioti, 2016	26	34	Clindamycin 600mg and rifampicin 600mg for 12 weeks	PGA of inflammatory lesions (abscesses, inflammatory nodules). Response defined as at least 50% clinical improvement from baseline.	19/26 (73%) clinical response	8/26, nausea and vomiting (8)	10 relapsed after a mean of 4.2 months	Prospective observational	IV
Caro, 2018	30	36	Clindamycin 600mg and rifampicin	Hurley, IHS4, DLQI, Pain VAS, Sonographic	17/30 (57%) HiSCR	7/30, diarrhea (6), candida vaginitis(1)	15/30 patients relapsed	Retrospective observational	III-3

SKIN

			600mg for 8 weeks	scoring, HiSCR measure			after mean 12.4 weeks		
Ochi, 2018	11	25	Clindamycin 600mg and rifampicin 600mg for 10 weeks	HS PGA	7/11 (64%) improved	1/11, nausea and vomiting (1)	NR	Retrospective observational	IV
Marasca, 2019	30	24	Clindamycin 600mg and rifampicin 600mg for 10 weeks	MSS, hidradisk score, HiSCR	Significant improvement in MSS and hidradisk score; 10/30 (33%) HiSCR	2/30, nausea and vomiting (2)	NR	Retrospective observational	III-3
Caro, 2020	26	36	Clindamycin 600mg and rifampicin 600mg for 10 weeks	Hurley, IHS4, DLQI, Pain VAS, Sonographic scoring, HiSCR measure	14/26 (54%) HiSCR	8/26 diarrhea (6), candida vaginitis (2)	68% of patients relapsed after mean 24.9 weeks	Retrospective observational	III-3
Iannone, 2021	19	31	Clindamycin 600mg and rifampicin 600mg for 12 weeks	MSS, DLQI, AISI	Mean MSS reduction of 68.5%	6/26 diarrhea (6),	Mean number of flares in 6 months was 3	Retrospective observational	III-3
Van Straalen, 2021	103	36 (27-45)^	Clindamycin 600mg and rifampicin 600mg for 12 weeks	NRS pain, NRS pruritus, DLQI, nodule count, abscess count, draining sinus count, IHS4, MSS, Hurley, HiSCR	40/103 (48%) HiSCR	34/103, diarrhea (18)	NR	Prospective observational	III-3
Yao, 2021	54	39.1	Clindamycin 600mg and rifampicin 600mg for 6 months	HSS, DLQI, VAS, PGA	7/54 (13%) full remission, significant improvement in HSS	30/54, diarrhea (12), abdominal pain (9), nausea (6), fatigue/general discomfort (7)	NR	Prospective observational	III-3

Rifampicin + moxifloxacin + metronidazole									
Join-Lambert, 2011	28	30	IV ceftriaxone and oral metronidazole for 3 weeks followed by rifampicin (10mg/kg), moxifloxacin (400mg) and metronidazole (1500mg) for 6 weeks	Complete remission (no active lesions); partial remission (decrease in Hurley stage or number of affected sites) Sartorius score, pain score, Skindex-France questionnaire, number of lesions	16/28 (57%) complete remission; 12/28 partial remission (43%)	18/28, nausea and diarrhea (18), vaginal candidiasis (7), moxifloxacin tendinitis (4)	7/28 patients relapsed at 12 months	Retrospective observational	IV
Delage, 2020	28	32	Rifampicin (10mg/kg), moxifloxacin (400mg) and metronidazole (1500mg) for 6 weeks followed by Rifampicin (10mg/kg) and moxifloxacin (400mg) for 4 weeks	Complete remission (no active lesions); partial remission (decrease in Hurley stage or number of affected sites) Sartorius score, pain score, Skindex-France questionnaire, number of lesions	Significant improvement in Sartorius, pain VAS and Skindex score, 21/28 (75%) clinical remission	27/28, mild digestive discomfort (27), mucosal candidiasis (18), asthenia (22)	Sustained results after 1 year	Prospective observational	III-3
Combinations with at least one antibiotic									
Scheinfield, 2015	1	57	IV linezolid (1.2g) and meropenem (1g) for 1 month	Hurley, clinical findings	1/1 (100%) complete remission	0/1	Relapse after 2 weeks	Case report	IV
Armyra, 2017	20	40	Minocycline (100mg) and colchicine (1mg) daily for 6 months	Hurley, PGA, DLQI	Improvement in PGA and DLQI in all patients	3/20, nausea and diarrhea (3)	Sustained results at 9 months	Prospective observational	IV

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Delaunay, 2018	65	23.4	Ofloxacin and clindamycin of various dosages for mean of 4.3 months	Hurley, complete remission (no flare), partial remission (partial reduction)	22/65 (34%) complete remission; 16/65 (25%) partial remission	18/65, worsening renal function and anemia (8), diarrhea (5)	NR	Retrospective observational	IV
Fania, 2020	36	38	Triamcinolone 40 mg and lincomycin 600 mg injection at 0 and 2 weeks	Hurley, Sartorius, Clinical score, SF-36, Skindex-17, pain VAS, GHQ-12	Significant improvement of clinical, pain VAS,	3/36, fever (1), delayed menses (1), acanthosis nigricans (1)	NR	Prospective observational	IV
Other combination treatments									
Hessam, 2016	66	39	Zinc gluconate (90mg/day) and topical triclosan (2%) twice daily for 12 weeks	MHSS (modified HS score), Hurley, DLQI, clinical findings, pain VAS	Significant improvement of mHSS, No. inflammatory nodules, new boils or flares	12/54	No change in results at 6 months	Retrospective observational	IV
McPhie, 2019	31	38	Various treatment combination, doses and duration	Hurley, IHS4	Reduction of Mean IHS4 by 9.87	NR	NR	Retrospective observational	IV
Brunasso, 2008	7	40	Infliximab (5mg/kg) at weeks 0, 2 and 6 and every 8 weeks and methotrexate (7.5mg) once weekly for mean 58.6 weeks	Area affected, Pain and discharge VAS, DLQI	Significant improvement in affected area and pain, discharge and DLQI scores	NR	After 24 months pain, QoL scores and area affected reduction increased	Retrospective observational	IV
Kozub, 2012	1	53	Infliximab (500mg) every 8 weeks and	Clinical findings, CRP	CRP significantly decreased	NR	Normal CRP levels at 43 weeks	Case report	IV

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			dapsone (100- 200mg/day) for 16 weeks						
Bettuzzi, 2020	9	29 (27-34) [^]	Sirolimus and TNF inhibitors (dosing NR)	HS-PGA, DLQI, VAS, CRP	2/9 complete response, 5/9 major response	1/9, erysipelas (1)	Sustained results at 15 months [^]	Retrospective Observationa I	IV

NR: not reported, PGA: physician's global assessment, IHS4: International Hidradenitis Suppurativa Severity Score System, DLQI: Dermatology Quality of Life Index, VAS: visual analogue scale, HiSCR: Hidradenitis suppurativa clinical response, MSS: modified Sartorius score, SF-36: 36-Item Short Form Health Survey questionnaire, mHSS: Modified Hidradenitis Suppurativa Score, CRP: C-reactive protein. AISI (acne inversa severity index). * Level of evidence is defined according to the National and Medical Research Council guidelines⁴⁷ [^]Median and range.