The efficacy and tolerability of tetracyclines and clindamycin plus rifampicin for the treatment of hidradenitis suppurativa: Results of a prospective European cohort study

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Background: Tetracyclines and clindamycin plus rifampicin combination therapy are both considered first-line therapy in current hidradenitis suppurativa guidelines. However, evidence for their efficacy is drawn from small studies, often without validated outcomes.

Objective: To assess the 12-week efficacy of oral tetracyclines and a combination of clindamycin and rifampicin.

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Methods: A prospective, international cohort study performed between October 2018 and August 2019.

Results: In total, 63.6% of the included 283 patients received oral tetracyclines, and 36.4% were treated with clindamycin and rifampicin. Both groups showed a significant decrease in International Hidradenitis Suppurativa Severity Score System from baseline (both $P < .001$). The Hidradenitis Suppurativa Clinical Response (HiSCR) was achieved in 40.1% and 48.2% of patients, respectively ($P = .26$). Patient characteristics or disease severity were not associated with the attainment of HiSCR or the minimal clinically important differences for the Dermatology Life Quality Index and pain.

Limitations: Cohort study. Respectively, 23.9% and 19.4% of patients had to be excluded from the HiSCR analysis for the tetracycline and combination therapy group because of a low abscess and nodule count at baseline.

Conclusion: This study shows significant efficacy of both tetracycline treatment and clindamycin and rifampicin combination therapy after 12 weeks in patients with hidradenitis suppurativa. No significant differences in efficacy were observed between the 2 treatments, regardless of disease severity. (J Am Acad Dermatol 2021;85:369-78.)

Key words: acne inversa; antibiotics; clindamycin; doxycycline; efficacy; guideline; minocycline; outcome; rifampicin; tetracycline; therapy; treatment.

CAPSULE SUMMARY

- Evidence for the efficacy of tetracyclines and clindamycin plus rifampicin in hidradenitis suppurativa is drawn from small studies, often without validated outcomes.
- Both treatment with tetracyclines and clindamycin combined with rifampicin show significant efficacy in patients with hidradenitis suppurativa. No significant differences in efficacy were observed, regardless of disease severity.

Hidradenitis suppurativa (HS) is a chronic, autoinflammatory skin disease characterized by painful, deep-seated, highly inflamed nodules and draining tunnels in the intertriginous areas of the body.[1-3] Traditionally, HS has been treated with systemic antibiotics, which remain the first-line medical therapy to date. Current guidelines and consensus statements on the treatment of HS consistently recommend 2 types of antibiotic therapy as the first-line treatment.[4-11] Oral tetracyclines, such as doxycycline and minocycline, are recommended as a first-line therapy for mild to moderate HS.[4-11] The combination of clindamycin and rifampicin is favored as a first-line therapy for moderate to severe HS but is also recommended as a second-line therapy for mild to moderate disease unresponsive to oral tetracyclines before biologic treatment.[4-11]

Even though these treatments are considered first-line therapy, the evidence to support their efficacy is weak. Oral tetracycline has been studied in an small randomized controlled trial, showing similar efficacy to topical clindamycin.[12] The efficacy of clindamycin and rifampicin combination therapy is derived from several small retrospective and prospective case series.[13-22] Therefore, the aim of this multicenter, international study was to assess the 12-week efficacy of oral tetracyclines and a combination of clindamycin and rifampicin using validated and clinically meaningful physician and patient reported outcomes in patients with HS. In addition, we aimed to identify factors associated with treatment response.

MATERIALS AND METHODS

Study design

A detailed protocol including study design, inclusion and exclusion criteria, HS treatment guidelines, assessment schedule, and timeline was sent out in October 2018 to all centers that previously participated in an European Hidradenitis Suppurativa Foundation consortium study.[5,11]

Participants

Following this protocol, patients who were treated according to the current international guidelines with either oral tetracyclines (tetracycline 500 mg twice daily, doxycycline 100 mg once daily, minocycline 100 mg once daily) or clindamycin 300 mg twice daily in combination with rifampicin 600 mg a day in daily practice were included from 15 European centers between October 2018 and August 2019. Patients were included in a real-life clinical practice setting without blinding or randomization. Exclusion criteria were concomitant systemic therapy or invasive treatment (deroofing, excision,

Abbreviations used:

BMI: body mass index
CI: confidence interval
DLQI: Dermatology Life Quality Index
HiSCR: Hidradenitis Suppurativa Clinical Response
HS: hidradenitis suppurativa
IHS4: International Hidradenitis Suppurativa Severity Score System
MCID: minimal clinical important difference
NRS: Numerical Rating Scale
OR: odds ratio
PROM: patient-reported outcome measure

laser therapy, incision and drainage procedure, or intralesional corticosteroids) during the 12 weeks and missing lesion counts at either baseline or follow-up. Patient characteristics (age, sex, body mass index [BMI], disease duration, first or second degree family history) were collected at baseline. Patient-reported outcome measures (PROMs) (Numerical Rating Scale [NRS] pain, NRS Pruritus, and Dermatology Life Quality Index [DLQI]), and physician scores (inflammatory nodule count, abscess count, draining sinus tract count, International Hidradenitis Suppurativa Severity Score System [IHS4], modified Sartorius score, Hurley and refined Hurley staging) were assessed at baseline and after 12 weeks of treatment.[23-25] Hidradenitis Suppurativa Clinical Response (HiSCR), (50% or greater reduction in inflammatory lesion count [abscesses plus inflammatory nodules] and no increase in abscesses or draining fistulas compared with baseline) was calculated at 12 weeks.[26]

The minimal clinical important difference (MCID) was calculated for the DLQI score (≥4 point reduction from baseline) and for NRS Pain (≥30% and ≥1 point reduction from baseline).[27,28] MCIDs were considered missing when a patient did not meet the baseline requirements for MCID calculations—that is, DLQI score of less than 4 and NRS Pain score of less than 3. HiSCR was calculated for patients with a baseline abscess and nodule count of 3 or greater.[26] Patients who discontinued treatment were deemed to have not achieved HiSCR, MCID DLQI, and MCID NRS Pain.

Statistical analyses

Patient characteristics are presented as number (percentage) for categorical variables and as mean ± standard deviation or median (interquartile range), where appropriate for continuous variables. Normality was assessed by using the Kolmogorov-Smirnov test. Differences in patient characteristics, PROMs, and physician scores between treatment groups were assessed by using independent Student *t* tests or Mann-Whitney *U* tests for continuous variables and chi-square tests or the Fisher exact test for categorical variables, where appropriate. Change from baseline after 12 weeks of treatment was assessed by using paired *t* tests or Wilcoxon's signed rank test for continuous variables. Univariate logistic regression models were constructed to assess the association of antibiotic treatment and HiSCR, MCID DLQI, and MCID NRS Pain attainment and to identify factors associated with treatment response.

RESULTS

In total, 283 patients were included; 63.6% (180/283) patients received tetracycline treatment (tetracycline, n = 42; doxycycline, n = 121; minocycline, n = 17) and 36.4% (103/283) patients received treatment with a combination of clindamycin plus rifampicin. There were no significant differences between these 2 treatment groups regarding sex, age, age at onset, disease duration, BMI, smoking status, family history of HS, or previous surgical treatment (Table I). Patients treated with clindamycin and rifampicin had significantly more severe disease reflected in a significantly higher number of inflammatory nodules ($P = .029$) and draining sinus tracts ($P = .003$), higher IHS4 score ($P = .019$), Hurley stage ($P = .004$), modified Sartorius ($P = .001$), and NRS Pain score ($P = .005$) compared with patients treated with tetracycline.

Both groups showed a significant decrease in IHS4 from baseline; from a median (interquartile range) of 9.0 (5.0-18.5) to 5.0 (2.0-12.0) ($P < .001$) in the tetracycline group and from 13.0 (6.0-27.0) to 6.0 (1.0-17.0) ($P < .001$) in the combination therapy (Table II and Fig 1). Reductions in all lesion counts were observed (inflammatory nodules, abscesses, and draining tunnels). There was no significant difference in the percentage of patients achieving HiSCR between the tetracycline group (40.1%) and the clindamycin and rifampicin group (48.2%; $P = .263$) (Table II). HiSCR attainment was not related to Hurley stage or IHS4 category for either tetracyclines ($P = .920$ and $P = .495$) and clindamycin and rifampicin ($P = .807$ and $P = .796$); see Tables III and IV.

Patients in both groups reported a significant decrease in DLQI, NRS Pain, and NRS pruritus after 12 weeks of treatment (Table II and Fig 1). There was no significant difference between the treatment groups regarding the percentage of patients who achieved either the MCID for NRS Pain or the MCID for the DLQI ($P = .643$ and $P = .084$, respectively). MCID pain was significantly more often achieved by

Table I. Baseline characteristics

Patient characteristics	Tetracyclines (n = 180)	Clindamycin and rifampicin (n = 103)	*P* value
Female sex, n (%)	106 (58.9)	56 (54.4)	.533
Age, y, median (IQR)	37 (26-46)	36 (27-45)	.917
Missing, n	0	1	
Age at onset, y, median (IQR)	21 (15-30)	21 (16-28)	.854
Missing, n	3	0	
Disease duration, median (IQR)	10 (6-19)	10 (5-17)	.415
Missing, n	3	1	
BMI, kg/m^2, mean (SD)	29.81 (6.1)	29.21 (6.2)	.428
Missing, n	6	0	
Current smoker, n (%)	110 (61.8)	56 (56.6)	.443
Missing, n	2	4	
Family history of HS, n (%)	58 (34.3)	34 (35.1)	1.000
Missing, n	11	6	
Previous surgical treatment, n (%)	69 (38.3)	39 (38.6)	1.000
Missing, n	0	2	
Patient-reported outcomes			
DLQI, mean (SD)	13.3 (7.5)	15.1 (7.9)	.071
Missing, n	8	7	
NRS Pain, median (IQR)	6 (4-8)	7 (5-8)	**.005**
Missing, n	7	3	
NRS Pruritus, median (IQR)	3 (0-6)	4 (0-7)	.204
Missing, n	13	8	
Physician scores			
Inflammatory nodules, median (IQR)	3.5 (1.0-6.0)	4 (2-9)	**.029**
Abscesses, median (IQR)	0.0 (0.0-2.0)	0 (0-2)	.975
Draining sinus tracts, median (IQR)	1.0 (0.0-2.0)	1 (0-4)	**.003**
Hurley stage			
Stage I, n (%)	54 (30.2)	14 (13.6)	**.004**
Stage II, n (%)	90 (50.3)	58 (56.3)	
Stage III, n (%)	35 (19.5)	31 (30.1)	
Missing, n	1	0	
Refined Hurley stage			
Stage Ia, n (%)	22 (12.3)	2 (1.9)	**.004**
Stage Ib, n (%)	24 (13.4)	9 (8.7)	
Stage Ic, n (%)	17 (9.5)	11 (10.7)	
Stage IIa, n (%)	22 (12.3)	6 (5.8)	
Stage IIb, n (%)	42 (23.5)	25 (24.3)	
Stage IIc, n (%)	29 (16.2)	28 (27.2)	
Stage III, n (%)	23 (12.8)	22 (21.4)	
Missing, n	1	0	
IHS4, median (IQR)	9.0 (5.0-18.5)	13.0 (6.0-27.0)	**.019**
Mild, n (%)	29 (16.1)	8 (7.8)	**.032**
Moderate, n (%)	77 (42.8)	38 (36.9)	
Severe, n (%)	74 (41.1)	57 (55.3)	
Modified Sartorius, median (IQR)	25.5 (17.0-44.0)	40.0 (26.0-59.0)	**<.001**
Missing, n	38	46	

Bold indicates significant *P* value $\leq$ .05.

BMI, Body mass index; *DLQI,* Dermatology Quality of Life Index; *HS,* hidradenitis suppurativa; *IHS4,* International Hidradenitis Suppurativa Scoring System; *IQR,* interquartile range; *NRS,* Numerical Rating Scale; *SD,* standard deviation.

patients in Hurley stage III or IHS4 severe category (respectively, $P = .028$ and $P = .001$) in the tetracycline group. No significant difference for MCID pain attainment was found in the clindamycin and rifampicin group.

Univariate regression analysis showed no significant difference between treatment with tetracycline or clindamycin and rifampicin regarding attainment of either HiSCR, MCID NRS Pain, or MCID DLQI: respectively, odds ratio [OR], 1.39 (95% confidence

Table II. Response to treatment after 12 weeks

Outcomes	Tetracyclines (n = 180)	*P* value*	Clindamycin and rifampicin (n = 103)	*P* value*	*P* value†
Patient-reported outcomes					
DLQI, mean (SD)	10.2 (8.2)	**<.001**	9.8 (7.6)	**<.001**	
Missing, n	7		3		
DLQI MCID achieved, n (%)	58 (36.3)		44 (47.3)		.084
Missing, n	20		10		
NRS Pain, median (IQR)	4.0 (1.5-7.0)	**<.001**	3 (0.0-5.5)	**<.001**	
Missing, n	4		3		
NRS Pain MCID achieved	58 (59.8)		51 (63.8)		.643
Missing, n	83		23		
NRS Pruritus, median (IQR)	1.0 (0.0-5.0)	**<.001**	1.0 (0.0-5.0)	**<.001**	
Missing, n	12		8		
Physician scores					
Inflammatory nodule count, median (IQR)	2.0 (0.0-4.0)	**<.001**	2.0 (0.0-4.0)	**<.001**	
Abscess count, median (IQR)	0.0 (0.0-1.0)	**<.001**	0.0 (0.0-1.0)	**.001**	
Draining sinus tract count, median (IQR)	0.0 (0.0-2.0)	**<.001**	1.0 (0.0-2.0)	**<.001**	
IHS4, median (IQR)	5.0 (2.0-12.0)	**<.001**	6.0 (1.0-17.0)	**<.001**	
Mild, n (%)	58 (32.2)		34 (33.0)		
Moderate, n (%)	70 (38.9)		29 (28.2)		
Severe, n (%)	52 (28.9)		40 (38.8)		
Modified Sartorius, median (IQR)	17.0 (10.0-35.0)	**<.001**	25.0 (13.0-44.0)	**<.001**	
Missing, n	41		45		
HiSCR achieved	55 (40.1)		40 (48.2)		.263
Missing because of baseline count <3, n	43		20		
Discontinuation and side effects					
Discontinuation	19 (10.7)		16 (15.8)		.260
Missing, n	3		2		
Gastrointestinal adverse effects not leading to discontinuation	24 (16.4)		10 (11.8)		.346
Missing	34		18		

Bold indicates significant *P* values.

DLQI, Dermatology Quality of Life Index; *HiSCR,* Hidradenitis Suppurativa Clinical Response; *IHS4,* International Hidradenitis Suppurativa Scoring System; *IQR,* interquartile range; *MCID,* minimal clinically important difference; *NRS,* numerical rating scale; *SD,* standard deviation.

*Compared with baseline scores.

†Comparison of tetracycline and clindamycin plus rifampicin groups.

interval (CI), 0.80-2.40; *P* = .243); OR, 1.58 (95% CI, 0.94-2.65; *P* = .085); and OR, 1.18 (95% CI, 0.64-2.18; *P* = .590); see Table III. HiSCR attainment was not associated with specific patient characteristics, baseline PROMs, or physician scores for either tetracycline or clindamycin and rifampicin treatment (Supplemental Tables I and II; available via Mendeley at https://doi.org/10.17632/xkz8rfyvdp.1). Baseline inflammatory nodule count was significantly associated with MCID NRS Pain attainment in both the tetracycline and the combination treatment group: respectively, OR, 1.15 (95% CI, 1.02-1.30; *P* = .023) and OR, 1.11 (95% CI, 1.01-1.23; *P* = .034); see Supplemental Tables I and II.

Gastrointestinal adverse effects, not leading to treatment discontinuation, were reported by 16.4% of patients in the tetracycline group compared with 11.8% of patients in the combination treatment group (*P* = .346). The percentage of participants discontinuing either tetracycline treatment (10.7%) or clindamycin and rifampicin treatment (15.8%) because of effects did not differ significantly (*P* = .260).

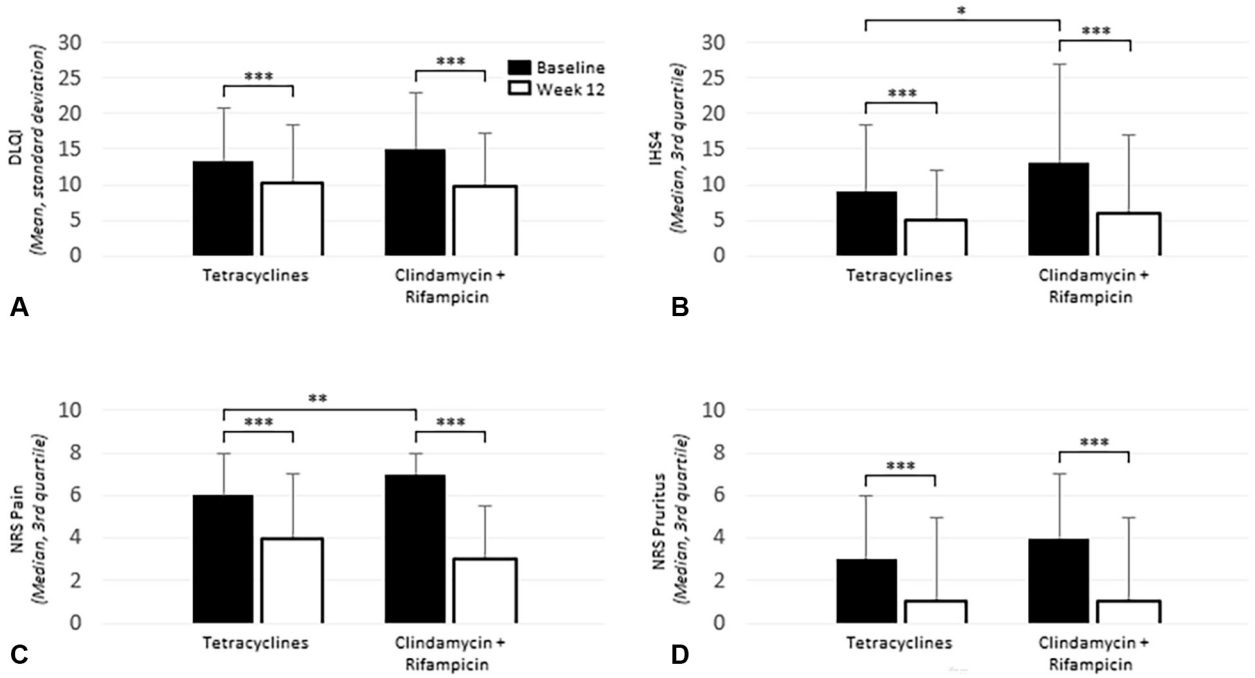

Fig 1. Response after 12 weeks of treatment. **A**, DLQI. **B**, IHS4. **C**, NRS Pain. **D**, NRS Pruritus. *DLQI,* Dermatology Quality of Life Index; *IHS4,* International Hidradenitis Suppurativa Scoring System; *NRS,* Numerical Rating Scale. *$P < .05$, **$P < .01$, ***$P < .001$.

Table III. Response to treatment per disease severity category

	Hurley stage I	Hurley stage II	Hurley stage III	*P* value	IHS4 mild	IHS4 moderate	IHS4 severe	*P* value
Tetracyclines, n	54*	90*	35*		29	77	74	
HiSCR achieved, n (%)	15 (39.5)	30 (41.7)	10 (37.0)	.920	5 (41.7)	20 (34.5)	30 (44.8)	.495
Missing, n	16	18	8		17	19	7	
MCID DLQI achieved, n (%)	20 (41.7)	28 (35.4)	10 (31.3)	.629	9 (31.0)	25 (32.5)	24 (34.3)	.901
Missing, n	6	11	3		6	10	4	
MCID Pain achieved, n (%)	13 (41.9)	29 (64.4)	16 (76.2)	**.028**	3 (23.1)	19 (51.4)	36 (76.6)	**.001**
Missing, n	23	45	14		16	40	27	
Clindamycin plus rifampicin, n	14	58	31		8	38	57	
HiSCR achieved, n (%)	3 (37.5)	24 (51.1)	13 (46.4)	.807	1 (25.0)	12 (48.0)	27 (50.0)	.796
Missing, n	6	11	3		4	13	3	
MCID DLQI achieved, n (%)	6 (54.5)	25 (49.0)	13 (41.9)	.763	2 (33.3)	16 (47.1)	26 (49.1)	.843
Missing, n	3	7	0		2	4	4	
MCID Pain achieved, n (%)	5 (62.5)	28 (62.2)	18 (66.7)	.941	2 (40.0)	17 (58.6)	32 (69.6)	.357
Missing, n	6	13	4		3	9	11	

Bold indicates significant *P* values.
DLQI, Dermatology Quality of Life Index; *HiSCR,* Hidradenitis Suppurativa Clinical Response; *IHS4,* International Hidradenitis Suppurativa Scoring System; *MCID,* minimal clinically important difference.
*Hurley stage missing for 1 patient on tetracyclines.

No significant associations were found for BMI, age, smoking status, discontinuation of treatment, or gastrointestinal adverse effects for either tetracycline or combination treatment, (data not shown). Women more often reported gastrointestinal adverse effects compared with men when treated with tetracyclines: OR, 2.81 (95% CI, 1.04-7.56; $P = .041$). No such association was found for treatment with clindamycin and rifampicin.

DISCUSSION

This multicenter, prospective study shows significant reduction in IHS4, pain, and DLQI scores after 12 weeks of treatment with both tetracyclines

Table IV. Regression analysis of validated outcomes

	HiSCR			MCID DLQI			MCID pain		
	n	OR (95% CI)	*P* value	n	OR (95% CI)	*P* value	n	OR (95% CI)	*P* value
Antibiotic treatment	220	1.39 (0.80-2.40)	.243	253	1.58 (0.94-2.65)	.085	177	1.18 (0.64-2.18)	.590
Patient characteristics									
Sex*	220	1.03 (0.60-1.77)	.910	253	0.98 (0.59-1.62)	.928	177	0.97 (0.52-1.79)	.915
Age	219	1.02 (1.00-1.04)	.051	252	1.00 (0.99-1.03)	.395	177	1.03 (1.00-1.05)	**.042**
Age at onset	218	1.02 (0.99-1.05)	.126	250	1.00 (0.98-1.03)	.855	176	1.03 (1.00-1.07)	.051
Disease duration	217	1.02 (0.99-1.05)	.291	249	1.01 (0.99-1.04)	.257	176	1.00 (0.98-1.03)	.782
BMI	215	0.99 (0.95-1.04)	.786	247	0.96 (0.96-1.04)	.799	173	1.00 (0.94-1.05)	.858
Smoking status*	218	1.35 (0.78-2.36)	.286	250	1.34 (0.80-2.27)	.271	174	2.03 (1.09-3.80)	**.026**
Family history of HS*	208	1.02 (0.57-1.81)	.955	238	1.07 (0.62-1.83)	.820	165	1.15 (0.60-2.22)	.673
Previous surgical treatment*	219	1.14 (0.66-1.96)	.644	251	1.21 (0.72-2.02)	.468	175	1.63 (0.86-3.09)	.138
Patient-reported outcome measures at baseline									
DLQI	211	1.04 (1.00-1.07)	.053	251	1.11 (1.07-1.16)	<.001	170	1.02 (0.98-1.07)	.305
NRS Pain	216	1.03 (0.93-1.14)	.601	250	1.06 (0.97-1.17)	.215	176	1.01 (0.88-1.16)	.867
NRS Pruritus	208	1.07 (0.98-1.16)	.131	240	1.11 (1.03-1.20)	.009	169	1.07 (0.97-1.18)	.154
Physician scores at baseline									
Inflammatory nodule count	220	1.06 (1.00-1.12)	**.044**	253	1.03 (0.98-1.08)	.299	177	1.13 (1.05-1.22)	**.002**
Abscess count	220	0.96 (0.87-1.07)	.473	253	1.06 (0.96-1.17)	.271	177	1.18 (1.02-1.37)	**.026**
Draining sinus tract count	220	0.96 (0.87-1.04)	.340	253	0.92 (0.84-1.00)	.054	177	1.06 (0.94-1.19)	.328
Presence of sinus tracts	220	0.90 (0.52-1.54)	.690	253	0.78 (0.47-1.31)	.352	177	1.36 (0.73-2.54)	.332
Hurley stage									
Hurley stage I		Reference			Reference			Reference	
Hurley stage II	220	1.22 (0.71-2.08)	.475	252	1.03 (0.62-1.70)	.922	177	1.16 (0.63-2.13)	.626
Hurley stage III	220	0.93 (0.50-1.72)	.814	252	0.80 (0.44-1.44)	.459	177	1.75 (0.86-3.57)	.125
IHS4	220	1.00 (0.98-1.01)	.677	253	0.99 (0.98-1.01)	.331	177	1.03 (1.01-1.05)	**.017**
Mild		Reference			Reference			Reference	
Moderate	220	0.74 (0.42-1.28)	.281	253	1.02 (0.61-1.70)	.941	177	0.63 (0.34-1.17)	.139
Severe	220	1.43 (0.83-2.45)	.194	253	1.03 (0.62-1.70)	.916	177	2.85 (1.52-5.34)	**.001**
Modified Sartorius	161	0.99 (0.98-1.00)	.100	183	0.99 (0.98-1.00)	.054	122	1.00 (0.98-1.01)	.603

Bold indicates significant *P* values.
BMI, Body mass index; *CI,* confidence interval; *DLQI,* Dermatology Quality of Life Index; *HiSCR,* Hidradenitis Suppurativa Clinical Response; HS, hidradenitis suppurativa; *IHS4,* International Hidradenitis Suppurativa Scoring System; *MCID,* minimal clinically important difference; *NRS,* Numerical Rating Scale; *OR,* odds ratio.
*Reference categories: female, nonsmokers, no family history, no previous surgical treatment.

treatment and clindamycin and rifampicin combination therapy. The use of tetracyclines in HS is derived from a small randomized controlled trial showing equal efficacy of oral tetracyclines and topical clindamycin in patients with mild to moderate HS using a nonvalidated outcome.[12] More recently, HiSCR response was assessed in a retrospective case series of patients treated with systemic doxycycline 100 mg twice daily, with 60% of patients achieving HiSCR after 12 weeks of treatment.[14] This is markedly higher than the 40.1% HiSCR attainment found in the tetracycline group in our study. However, no baseline abscess and nodule count was reported by Vural et al,[14] which is known to influence HiSCR attainment, and the included population may not be comparable to that of our study. Nonetheless, doxycycline has previously been shown to have a dose-response effect in reducing inflammatory lesions in patients with moderate to severe acne vulgaris.[29] Because the same mechanisms of the effect of tetracyclines (antibacterial and anti-inflammatory) are assumed in acne and HS, a similar dose-response effect in HS is conceivable.

Current guidelines advise the use of clindamycin 300 mg twice daily and rifampicin 300 mg twice daily or 600 mg once daily for a duration of 10 to 12 weeks for moderate to severe HS.[30] Treatment with clindamycin and rifampicin has been previously assessed in 1 prospective and several smaller retrospective trials with differing types of administration (intravenous or oral), dosage (eg, 4 times 125 mg of clindamycin or 300 mg twice daily), and timing of the primary endpoint (ranging from 8 to 12 weeks).[13-22] Overall, HiSCR was achieved by 33.3% to 56.7% of patients treated with clindamycin plus rifampicin. Even though some of these studies

report excluding patients lost to follow-up from the efficacy analysis, potentially inflating response rates, our study found HiSCR attainment in the higher end of this range (48.2%). Severe HS might represent a specific subtype.[31] Contradictory results regarding an association between disease severity and clinical response have been reported. Caposiena Caro et al[15] found that HiSCR attainment on clindamycin plus rifampicin therapy was significantly more common in patients with mild and moderate disease, measured with both the Hurley stage and IHS4 (respectively, $P < .001$ and $P = .02$).[15] Our results show no association between disease severity and HiSCR attainment, similar to the results from Dessinioti et al.[18]

Current guidelines advise the use of a combination of clindamycin and rifampicin.[4-11] However, rifampicin has been shown to dramatically reduce plasma concentrations of clindamycin, making a meaningful contribution of clindamycin to either bacterial resistance or reduction of inflammation in this combination unlikely.[32] A retrospective study found similar rates of HiSCR attainment between treatment with clindamycin and rifampicin compared with clindamycin alone after 8 weeks of treatment: 56.7% versus 63.3% ($P = .598$), excluding patients who were lost to follow-up from the efficacy analysis.[19]

Even though there are validated MCID values for both the NRS Pain and the DLQI, only 1 registry study has published MCID results to date, with these lacking in the large randomized controlled trials.[26-28,33] Achieving the MCID, defined as the smallest change that a patient would identify as clinically meaningful, could be more informative and clinically relevant than the mean reductions in DLQI or pain scores frequently reported in HS clinical trials. Overall, in our study, approximately 60% of patients attained a clinically meaningful difference in NRS Pain, and between 36% and 47% achieved a meaningful improvement in DLQI score, with no significant differences between treatment groups.

Gastrointestinal adverse effects are a main concern because they often lead to discontinuation of treatment.[34,35] The frequency of gastrointestinal adverse effects in our study (11.8%) was lightly lower than those previously reported in a large retrospective study and the only prospective study on clindamycin and rifampicin to date at, respectively, 14% and 19.2%.[17,18] However, the discontinuation rate (15.8%) in our study was slightly higher than that seen in these studies, at 11.4% and 11.5% respectively. Interestingly, more gastrointestinal adverse effects, not leading to treatment discontinuation, were noted in the tetracycline group, whereas more treatment discontinuation was seen in the clindamycin and rifampicin group.

In the current HS treatment guidelines and consensus statements, tetracyclines are considered the first-line treatment for mild to moderate HS, whereas the combination of clindamycin and rifampicin is favored for moderate to severe HS.[4-11] Interestingly, our study showed no significant differences between the 2 antibiotic strategies for the validated outcomes HiSCR, MCID Pain, or MCID DLQI, even in patients with moderate to severe HS. These results suggest that tetracyclines could be considered as the first-line treatment in patients with moderate to severe disease. This could prove especially valuable in countries with endemic tuberculosis, where rifampicin is preferably reserved for the treatment of tuberculosis or in patients with relative contraindications because of potential drug interaction, such as, for example, oral contraceptives.[36] Moreover, guidelines advise that biologics (adalimumab) can be initiated after failure of conventional treatment, often clindamycin and rifampicin combination therapy.[4-11] However, because our study suggests that this treatment is similar to treatment with tetracyclines, failure of tetracycline treatment could be a sufficient indication for biologic eligibility. Nonetheless, a head-to-head randomized, blinded, controlled trial comparing tetracycline treatment with clindamycin and rifampicin combination therapy is needed to increase the evidence to a level where firmer conclusions can be drawn.

A limitation of this study is inherent to the calculation of the HiSCR. In accordance with its original publication, HiSCR can be calculated only in patients with 3 or more inflammatory lesions (abscesses and nodules) at baseline.[26] Overall, respectively, 23.9% and 19.4% of patients had to be excluded from the HiSCR analysis for the tetracycline and combination therapy group based on low abscess and nodule counts at baseline. However, this is not representative of real life and hampers the extrapolation of HiSCR results to routine clinical settings. This issue could potentially be overcome by a dichotomous version of the IHS4 score.

In conclusion, this study shows no significant difference between patients treated with tetracyclines or with a combination of clindamycin and rifampicin in the validated outcomes HiSCR, IHS4, MCID DLQI, and MCID Pain after 12 weeks, regardless of disease severity. These results might suggest that tetracyclines could be considered as the first-line treatment in patients with moderate to severe disease, and failure of tetracyclines may be a sufficient indication for the initiation of biologic therapy.

Conflicts of interest

Dr Tzellos has reported relationships with AbbVie, UCB, and Sanofi Genzyme. Dr Guillem has received honoraria from AbbVie and Novartis as a consultant and has given nonpaid lectures for AbbVie, Brothier, Cicaplus, Coloplast, Inresa, and Novartis. Dr Giamarellos-Bourboulis has received honoraria from Abbott CH, Angelini Italy, bioMérieux Inc, InflaRx GmbH, MSD Greece, and XBiotech Inc; independent educational grants from AbbVie, Abbott, Astellas Pharma Europe, AxisShield, bioMérieux Inc, InflaRx GmbH, ThermoFisher Brahms GmbH, and XBiotech Inc; and funding from the FrameWork 7 program HemoSpec (granted to the National and Kapodistrian University of Athens), the Horizon2020 Marie-Curie Project European Sepsis Academy (granted to the National and Kapodistrian University of Athens), and the Horizon 2020 European Grant ImmunoSep (granted to the Hellenic Institute for the Study of Sepsis). Dr Jemec has received honoraria from AbbVie, Chemocentryx, Coloplast, Incyte, Inflarx, Kymera, Leo Pharma, Novartis, and UCB for participation on advisory boards; grants from AbbVie, AstraZeneca, Inflarx, Janssen-Cilag, Leo Pharma, Novartis, Regeneron, and Sanofi for participation as an investigator; speaker honoraria from AbbVie, Boehringer Ingelheim, Galderma, and Novartis; and unrestricted departmental grants from Leo Pharma and Novartis. Dr Katoulis has reported relationships with AbbVie, Novartis, Genesis Pharma, Mylan, Janssen, Leo Pharma, and Lilly. Dr Koenig was an investigator, speaker, or advisor for AbbVie, Braun-Stiftung, and Celgene. Dr Lazaridou has received speaker honoraria, and/or honoraria for participation in advisory boards, and/or grants from AbbVie, Novartis, Genesis Pharma, Mylan, Pfizer, Janssen, Leo Pharma, Roche, Lilly, UCB, and Sanofi. Dr Matusiak reports personal fees from AbbVie, Amgen, Galapagos, InflaRx, Janssen-Cilag, LEO, Menlo, Novartis, Pfizer, Pierre Fabre, Regeneron, Trevi, and UCB. Dr Pinter has been an investigator, speaker, or advisor for AbbVie, Almirall-Hermal, Amgen, Biogen Idec, Biontec, Boehringer Ingelheim, Celgene, GlaxoSmithKline, Eli Lilly, Galderma, Hexal, Janssen, LEO-Pharma, MC2, Medac, Merck Serono, Mitsubishi, MSD, Novartis, Pascoe, Pfizer, Tigercat Pharma, Regeneron, Roche, Sandoz Biopharmaceuticals, Sanofi-Genzyme, Schering-Plough, and UCB Pharma. Dr Romani has reported relationships with AbbVie, Novartis, Leo Pharma, Janssen, Almirall, and Isdín. Dr Saunte was paid as a consultant for advisory board meeting by AbbVie, Janssen, Sanofi, and Leo Pharma and received speaker honoraria and/or grants from AbbVie, Pfizer, Galderma, Novartis, and Leo Pharma during the last 5 years. Dr Szepietowski reports personal fees from AbbVie, Amgen, Galapagos, InflaRx, Janssen-Cilag, LEO, Menlo, Novartis, Pfizer, Pierre Fabre, Regeneron, Sandoz, Sanofi, Sienna, Trevi, and UCB. Dr Trigoni has reported relationships with AbbVie, UCB, Novartis, and LEO. Dr Trigoni has reported relationships with AbbVie, UCB, Novartis, and LEO. Dr van der Zee has received honoraria from AbbVie. Drs van Straalen, Benhadou, Cuencia-Barrales, Daxhelet, Daoud, Efthymiou, Marzano, Molina-Leyva, Moltrasio, Potenza, Skroza, Stergianou, and Vilarrasa have no conflicts of interest to declare.

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