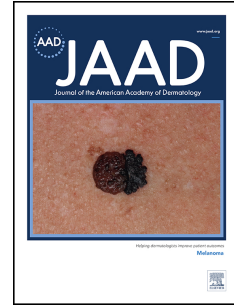


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The efficacy and tolerability of tetracyclines and clindamycin plus rifampicin for the treatment of hidradenitis suppurativa; results of a prospective European cohort study

K.R. van Straalen, MD, PhD, T. Tzellos, MD, PhD, P. Guillem, MD, PhD, F. Benhadou, MD, PhD, C. Cuenca-Barrales, MD, M. Daxhelet, MD, M. Daoud, MD, O. Efthymiou, MD, E.J. Giamarellos-Bourboulis, MD, PhD, G.B.E. Jemec, MD, DMSci, A.C. Katoulis, MD, A. Koenig, MD, PhD, E. Lazaridou, MD, PhD, A.V. Marzano, MD, Ł. Matusiak, MD, PhD, A. Molina-Leyva, MD, PhD, C. Moltrasio, MRes, A. Pinter, MD, PhD, C. Potenza, MD, J. Romaní, MD, PhD, D.M. Saunte, MD, PhD, N. Skroza, MD, D. Stergianou, MD, J. Szepietowski, MD, PhD, FRCP, A. Trigoni, MD, PhD, E. Vilarrasa, MD, H.H. van der Zee, MD, PhD

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

K.R. van Straalen^{1*} (MD, PhD), T. Tzellos^{2*} (MD, PhD), P. Guillem³ (MD, PhD), F. Benhadou⁴ (MD, PhD), C. Cuenca-Barrales^{5,6} (MD), M. Daxhelet⁴ (MD), M. Daoud⁴ (MD), O. Efthymiou⁷ (MD), E.J. Giamarellos-Bourboulis⁸ (MD, PhD), G.B.E Jemec⁹ (MD, DMSci), A.C. Katoulis⁷ (MD), A. Koenig¹⁰ (MD, PhD), E. Lazaridou¹¹ (MD, PhD), A.V. Marzano^{12,13} (MD), Ł. Matusiak¹⁴ (MD, PhD), A. Molina-Leyva^{5,6} (MD, PhD), C. Moltrasio^{12,15} (MRes), A. Pinter¹⁰ (MD, PhD), C. Potenza¹⁶ (MD), J. Romani¹⁷ (MD, PhD), D.M. Saunte⁹ (MD, PhD), N. Skroza¹⁶ (MD), D. Stergjanou⁸ (MD), J. Szepietowski¹⁴ (MD, PhD, FRCP), A. Trigoni¹¹ (MD, PhD), E. Vilarrasa (MD)¹⁸, H.H. van der Zee¹ (MD, PhD)

**Authors contributed equally to this manuscript*

1. Erasmus MC, University Medical Center Rotterdam, Department of Dermatology, The Netherlands.
2. Department of Dermatology, Nordland Hospital Trust, Bodø, Norway.
3. Department of Surgery, Clinique du Val d'Ouest (Lyon), ResoVerneuil (Paris) and Groupe de Recherche en Proctologie de la Société Nationale Française de ColoProctologie, Paris, France.
4. Department of Dermatology, Université Libre de Bruxelles, Erasme Hospital, Brussels, Belgium.
5. Department of Dermatology, Hospital Universitario Virgen de las Nieves, Granada, Spain.
6. TECe19-Clinical and Translational Dermatology Investigation Group Ibs. Granada, Spain.
7. Second Department of Dermatology and Venereology, National and Kapodistrian University of Athens, Medical School, "Attikon" General University Hospital, Athens, Greece.
8. Fourth Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Athens, Greece.
9. Department of Dermatology, Zealand University Hospital, Roskilde and Health Sciences Faculty, University of Copenhagen, Denmark.
10. Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt am Main, Germany.
11. Second Department of Dermatology and Venereology, Aristotle University of Thessaloniki, General Hospital Papageorgiou, Thessaloniki, Greece.
12. Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.
13. Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy.
14. Department of Dermatology, Venereology and Allergology, Medical University, Wrocław, Poland.
15. Department of Medical Surgical and Health Sciences, University of Trieste, Trieste, Italy.
16. Dermatology Unit 'Daniele Innocenzi', Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Polo Pontino-Latina, Italy.
17. Department of Dermatology, Corporació Sanitària Parc Taulí, Sabadell, Spain.
18. Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

43 Corresponding author:

44 H.H. van der Zee
45 Department of Dermatology,
46 Erasmus University Medical Center,
47 dr. Molewaterplein 40,
48 3015 GD Rotterdam, The Netherlands
49 tel: +31 10 704 0110
50 email: h.vanderzee@erasmusmc.nl
51

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100 **ORCID IDs**

101 K.R. van Straalen: 0000-0003-3305-3814, T. Tzellos: 0000-0003-2356-0847, P. Guillem: 0000-0002-
102 5449-3897, F. Benhadou: 0000-0002-4533-8297, C. Cuenca-Barrales: 0000-0001-7579-4931, M.
103 Daxhelet: 0000-0003-4506-6989, M. Daoud: 0000-0003-4188-1986, O. Efthymiou: 0000-0002-0466-
104 7553, E.J. Giamarellos-Bourboulis: 0000-0003-4713-3911, G.B.E Jemec: 0000-0002-0712-2540, A.
105 Koenig: 0000-0001-9969-2315, E. Lazaridou: 0000-0002-4072-3591, A.V. Marzano: 0000-0002-8160-
106 4169, Ł. Matusiak: 0000-0003-2067-4929, A. Molina-Leyva: 0000-0001-6882-2113, A. Pinter: 0000-
107 0002-1330-1502, C. Potenza: 0000-0002-6300-8697, J. Romaní: 0000-0002-6134-5155, D.M. Saunte:
108 0000-0001-7953-1047, N. Skroza: 0000-0003-4478-5404, D. Stergianou: 0000-0002-3014-3155, J.
109 Szepletowski: 0000-0003-0766-6342, A. Trigoni: 0000-0002-2202-2337, H.H. van der Zee: 0000-
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127 **Keywords:** acne inversa, treatment, therapy, antibiotics, tetracycline, doxycycline, minocycline,
128 clindamycin, rifampicin, efficacy, outcome, guideline

129 **ABSTRACT**

130 **Background:** Tetracyclines and clindamycin plus rifampicin combination therapy are both
131 considered first-line therapy in current Hidradenitis Suppurativa (HS) guidelines. However,
132 evidence for their efficacy is drawn from small studies, often without validated outcomes.

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

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

137 **Results:** In total, 63.6% of the included 283 patients received oral tetracyclines and 36.4%
138 were treated with clindamycin and rifampicin. Both groups showed a significant decrease in
139 IHS4 from baseline (both $p < 0.001$). HiSCR was achieved in 40.1% and 48.2% of patients,
140 respectively ($p = 0.26$). Patient characteristics or disease severity were not associated with
141 attainment of HiSCR or the minimal clinically important differences for the DLQI and pain.

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

145 **Conclusion:** This study shows significant efficacy of both tetracycline treatment and
146 clindamycin and rifampicin combination therapy after 12 weeks in patients with HS. No
147 significant differences in efficacy were observed between the two treatments, regardless of
148 disease severity.

149 INTRODUCTION

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

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

169

170 MATERIALS AND METHODS

171 *Study design*

172 A detailed protocol including study design, in- and exclusion criteria, HS treatment
173 guidelines, assessment schedule, and timeline and was sent out in October 2018 to all
174 centers who previously participated in an European Hidradenitis Suppurativa Foundation
175 consortium study.^{5,11}

176 *Participants*

177 Following this protocol, patients treated according to the current international guidelines with
178 either oral tetracyclines (tetracycline 500mg b.i.d, doxycycline 100mg once daily, minocycline
179 100mg once daily) or clindamycin 300mg b.i.d in combination with rifampicin 600mg a day in
180 daily practice were included from 15 European centers between October 2018 and August
181 2019. Patients were included in a real-life clinical practice setting without blinding or
182 randomization. Exclusion criteria were concomitant systemic therapy, invasive treatment
183 (deroofing, excision, laser therapy, incision and drainage procedure, or intralesional
184 corticosteroids) during the 12 weeks, and missing lesion counts at either baseline of follow-
185 up. Patient characteristics (age, gender, body mass index; BMI, disease duration, 1st or 2nd
186 degree family history) were collected at baseline. Patient reported outcome measures
187 (PROMs; numerical rating scale (NRS) pain, NRS pruritus, and Dermatological Life Quality
188 Index; DLQI), and physician scores (inflammatory nodule count, abscess count, draining
189 sinus tract count, International Hidradenitis Suppurativa Severity Score System; IHS4,
190 modified Sartorius score, Hurley and Refined Hurley staging) were assessed at baseline and
191 after 12 weeks of treatment.²³⁻²⁵ Hidradenitis Suppurativa Clinical Response (HiSCR; $\geq 50\%$
192 reduction in inflammatory lesion count (abscesses + inflammatory nodules) and no increase
193 in abscesses or draining fistulas compared with baseline) was calculated at 12 weeks.²⁶

194 Minimal clinical important difference (MCID) was calculated for the DLQI score (≥ 4
195 point reduction from baseline) and for NRS Pain ($\geq 30\%$ and ≥ 1 point reduction from
196 baseline).^{27,28} MCIDs were considered missing when patient did not meet baseline
197 requirements for MCID calculations; i.e. DLQI score < 4 and NRS pain score < 3 . HiSCR was
198 calculated for patients with a baseline abscess and nodule count of ≥ 3 .²⁶ Patients who
199 discontinued treatment were deemed non-achievers of HiSCR, MCID DLQI, and MCID NRS
200 Pain.

201

202

203

204 *Statistical analyses*

205 Patient characteristics are presented as number (percentage, %) for categorical variables
206 and as mean \pm standard deviation (SD) or median [interquartile range, IQR] where
207 appropriate for continuous variables. Normality was assessed using the Kolmogorov-Smirnov
208 test. Differences in patient characteristics, PROMs and physician scores between treatment
209 groups were assessed using independent Student t-tests or Mann-Whitney U tests for
210 continuous variables and Chi-square tests or Fisher's exact test for categorical variables,
211 where appropriate. Change from baseline after 12 weeks of treatment was assessed using
212 paired T-tests or Wilcoxon signed-rank test for continuous variables. Univariate logistic
213 regression models were constructed to assess the association of antibiotic treatment and
214 HiSCR, MCID DLQI, and MCID NRS Pain attainment as well as to identify factors associated
215 with treatment response.

216

217 **RESULTS**

218 In total 283 patients were included; 63.6% (180/283) patients received tetracycline treatment
219 (tetracycline n=42, doxycycline n=121, minocycline n=17) and 36.4% (103/283) patients
220 received treatment with a combination of clindamycin plus rifampicin. There were no
221 significant differences between these two treatment groups regarding gender, age, age of
222 onset, disease duration, BMI, smoking status, family history of HS, or previous surgical
223 treatment (Table 1). Patients treated with clindamycin and rifampicin had significantly more
224 severe disease reflected in a significantly higher number of inflammatory nodules ($p=0.029$)
225 and draining sinus tracts ($p=0.003$), higher IHS4 score ($p=0.019$), Hurley stage ($p=0.004$),
226 modified Sartorius ($p<0.001$), and NRS pain score ($p=0.005$) compared with patients treated
227 with tetracycline.

228 Both groups showed a significant decrease in IHS4 from baseline; from median of 9.0
229 [5.0-18.5] to 5.0 [2.0-12.0] ($p<0.001$) in the tetracycline group and from 13.0 [6.0-27.0] to 6.0
230 [1.0-17.0] ($p<0.001$) in the combination therapy (Table 2 and Figure 1). Reductions in all
231 lesion counts were observed (inflammatory nodules, abscesses, and draining tunnels) There

232 was no significant difference in the percentage of patients achieving HiSCR between the
233 tetracycline group (40.1%) and the clindamycin and rifampicin group (48.2%), $p=0.263$ (Table
234 2). HiSCR attainment was not related to Hurley stage or IHS4 category for either
235 tetracyclines ($p= 0.920$ and $p=0.495$) and clindamycin and rifampicin ($p=0.807$ and $p=0.796$),
236 see Table 3 and 4.

237 Patients in both groups reported a significant decrease in DLQI, NRS pain, and NRS
238 pruritus after 12 weeks of treatment (Table 2 and Figure 1). There was no significant
239 difference between the treatment groups regarding the percentage of patients that achieved
240 either the MCID for NRS pain or the MCID for the DLQI, $p= 0.643$ and $p=0.084$ respectively.
241 MCID pain was significantly more often achieved by patients in Hurley stage III or IHS4
242 severe category, respectively $p=0.028$ and $p=0.001$ in the tetracycline group. No significant
243 difference for MCID pain attainment was found in the clindamycin and rifampicin group.

244 Univariate regression analysis revealed no significant difference between treatment
245 with tetracycline or clindamycin and rifampicin regarding attainment of either HiSCR, MCID
246 NRS Pain, or MCID DLQI; respectively OR 1.39 (95% CI 0.80-2.40, $p=0.243$), OR 1.58 (95%
247 CI 0.94-2.65, $p=0.085$), and OR 1.18 (95% CI 0.64-2.18, $p=0.590$), see Table 3. HiSCR
248 attainment was not associated with specific patient characteristics, baseline PROMs or
249 physician scores for either tetracycline or clindamycin and rifampicin treatment
250 (Supplemental Table 1 and 2 available through [*Mendeley link*]). Baseline inflammatory
251 nodule count was significantly associated with MCID NRS Pain attainment in both the
252 tetracycline and the combination treatment group, respectively OR 1.15 (95% CI 1.02-1.30,
253 $p=0.023$) and OR 1.11 (95% CI 1.01-1.23, $p=0.034$), see Supplemental Table 1 and 2.

254 Gastrointestinal side effects, not leading to treatment discontinuation, were reported
255 by 16.4% of patients in the tetracycline group compared with 11.8% of the patients in the
256 combination treatment group, $p=0.346$. The percentage of participants discontinuing either
257 tetracycline treatment (10.7%) or clindamycin and rifampicin treatment (15.8%) due to side
258 effects did not differ significantly, $p=0.260$.

259 No significant associations were found for BMI, age, smoking status, discontinuation
260 of treatment, or gastrointestinal side effects for either tetracycline or combination treatment,
261 data not shown. Women more often reported gastrointestinal side effects compared with men
262 when treated with tetracyclines, OR 2.81 (95% CI 1.04-7.56, p=0.041). No such association
263 was found for treatment with clindamycin and rifampicin.

264

265 **DISCUSSION**

266 This multicenter, prospective study shows significant reduction in IHS4, pain and DLQI
267 scores after 12 weeks of treatment with both tetracyclines treatment and clindamycin and
268 rifampicin combination therapy. The use of tetracyclines in HS is derived from a small
269 randomized controlled trial showing equal efficacy of oral tetracyclines and topical
270 clindamycin in patients with mild-moderate HS using a non-validated outcome.¹² More
271 recently, HiSCR response was assessed in a retrospective case series of patients treated
272 with systemic doxycycline 100mg b.i.d, with 60% of patients achieving HiSCR after 12 weeks
273 of treatment.¹⁴ This is markedly higher than the 40.1% HiSCR attainment found in the
274 tetracycline group in our study. However, no baseline AN-count was reported by Vural et al.,
275 which is known to influence HiSCR attainment, and the included population may not be
276 comparable to our study.¹⁴ Nonetheless, doxycycline has previously been shown to have a
277 dose-response effect in reducing inflammatory lesions in patients with moderate to severe
278 acne vulgaris.²⁹ As the same mechanisms of effect of tetracyclines (anti-bacterial and anti-
279 inflammatory) are assumed in acne and HS, a similar dose-response effect in HS is
280 conceivable.

281 Current guidelines advice the use of clindamycin 300mg bid and rifampicin 300mg
282 twice daily or 600mg once daily for a duration of 10-12 weeks for moderate-to-severe HS.³⁰
283 Treatment with clindamycin and rifampicin has been previously assessed in one prospective
284 and several smaller retrospective trials with differing types of administration (IV or oral),
285 dosage (e.g. 4 times 125 mg of clindamycin or 300mg twice daily,) and timing of the primary

286 endpoint (ranging from 8 – 12 weeks).¹³⁻²² Overall, HiSCR was achieved by 33.3%-56.7% of
287 patients treated with clindamycin + rifampicin. Even though some of these studies report
288 excluding patients lost to follow-up from the efficacy analysis, potentially inflating response
289 rates, our study found HiSCR attainment in the higher end of this range (48.2%). Severe HS
290 might represent a specific subtype.³¹ Contradictory results regarding an association between
291 disease severity and clinical response have been reported. Caposiena Caro et al. found that
292 HiSCR attainment on clindamycin plus rifampicin therapy was significantly more common in
293 patients with mild and moderate disease, measured with both the Hurley stage and IHS4
294 (respectively $p < .001$ and $p = 0.02$).¹⁵ Our results show no association between disease
295 severity and HiSCR attainment, similar to the results from Dessinioti et al..¹⁸

296 Current guidelines advice the use of a combination of clindamycin and rifampicin.⁴⁻¹¹
297 However, rifampicin has been shown to dramatically reduce plasma concentrations of
298 clindamycin, making a meaningful contribution of clindamycin to either bacterial resistance or
299 reduction of inflammation in this combination unlikely.³² A retrospective study found similar
300 rates of HiSCR attainment between treatment with clindamycin and rifampicin compared with
301 clindamycin alone after eight weeks of treatment; 56.7% vs. 63.3% ($p = 0.598$), excluding
302 patients who were lost to follow-up from the efficacy analysis.¹⁹

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

311 Gastro-intestinal side effects are a main concern as they often lead to discontinuation
312 of treatment.^{34,35} The frequency of gastro-intestinal side effects in our study (11.8%) was
313 slightly lower than those previously reported in a large retrospective study and the only

314 prospective study on clindamycin and rifampicin to date, respectively 14% and 19.2%.^{17,18}
315 However, the discontinuation rate (15.8%) in our study was slightly higher than seen in these
316 studies, 11.4% and 11.5% respectively. Interestingly, more gastrointestinal side effects, not
317 leading to treatment discontinuation, were noted in the tetracycline group while more
318 treatment discontinuation was seen in the clindamycin and rifampicin group.

319 In the current HS treatment guidelines and consensus statements, tetracyclines are
320 considered first-line treatment for mild-to-moderate HS whereas the combination of
321 clindamycin and rifampicin is favored for moderate-to-severe HS.⁴⁻¹¹ Interestingly our study
322 revealed no significant differences between the two antibiotic strategies for the validated
323 outcomes HiSCR, MCID Pain, or MCID DLQI even in patients with moderate-to-severe HS.
324 These results suggest that tetracyclines could be considered as first-line treatment in
325 patients with moderate-to-severe disease. This could prove especially valuable in countries
326 with endemic tuberculosis where rifampicin is preferably reserved for the treatment of
327 tuberculosis or in patients with relative contraindications due to potential drug interaction
328 such as e.g. oral contraceptives.³⁶ Moreover, guidelines advice that biologics (adalimumab)
329 can be initiated after failure of conventional treatment, often clindamycin and rifampicin
330 combination therapy.⁴⁻¹¹ However, as our study suggests that this treatment is similar to
331 treatment with tetracyclines, failure on tetracycline treatment could be a sufficient indication
332 for biologic eligibility. Nonetheless, a head-to-head randomized, blinded controlled trial
333 comparing tetracycline treatment with clindamycin and rifampicin combination therapy is
334 needed to increase the evidence to a level where firmer conclusions can be drawn.

335 A limitation of this study is inherent to the calculation of the HiSCR. In accordance
336 with its original publication, HiSCR can only be calculated in patients with three or more
337 inflammatory lesions (abscesses and nodules) at baseline.²⁶ Overall, respectively 23.9% and
338 19.4% of patients had to be excluded from the HiSCR analysis for the tetracycline and
339 combination therapy group based on the low abscess and nodule count at baseline.
340 However, this is not representative of real life and hampers the extrapolation of HiSCR

341 results to routine clinical settings. This issue could potentially be overcome by a dichotomous
342 version of the IHS4 score.

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

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450 **TABLE LEGENDS**

451

452

453 **Table 1. Baseline characteristics**

454 BMI; body mass index, HS; Hidradenitis Suppurativa, DLQI; Dermatology Quality of Life Index, NRS; Numerical
 455 rating scale, IHS4; International Hidradenitis Suppurativa Scoring System

456

457 **Table 2. Response to treatment after 12 weeks**

458 DLQI; Dermatology Quality of Life Index, MCID; minimal clinically important difference, NRS; Numerical rating
 459 scale, IHS4; International Hidradenitis Suppurativa Scoring System, HiSCR; Hidradenitis Suppurativa Clinical
 460 Response.* compared with baseline scores, ^ comparison of tetracycline and clindamycin + rifampicin groups

461

462 **Table 3. Response to treatment per disease severity category**

463 MCID; minimal clinically important difference, DLQI; Dermatology Quality of Life Index, HiSCR; Hidradenitis
 464 Suppurativa Clinical Response. * Hurley stage missing for 1 patient on tetracyclines.

465

466 **Table 4. Regression analysis of validated outcomes**

467 OR; Odds ratio, MCID; minimal clinically important difference, DLQI; Dermatology Quality of Life Index, NRS;
 468 Numerical rating scale, BMI; body mass index, IHS4; International Hidradenitis Suppurativa Scoring System. *
 469 reference categories; female, non-smokers, no family history, no previous surgical treatment

470

471 **Supplemental Table 1. Identification of factors associated with response to**472 **tetracyclines**

473 OR; Odds ratio, MCID; minimal clinically important difference, DLQI; Dermatology Quality of Life Index, NRS;
 474 Numerical rating scale, BMI; body mass index, IHS4; International Hidradenitis Suppurativa Scoring System. *
 475 reference categories; female, non-smokers, no family history, no previous surgical treatment

476

477 **Supplemental Table 2. Identification of factors associated with response to**478 **clindamycin and rifampicin**

479 OR; Odds ratio, MCID; minimal clinically important difference, DLQI; Dermatology Quality of Life Index, NRS;
 480 Numerical rating scale, BMI; body mass index, IHS4; International Hidradenitis Suppurativa Scoring System. *
 481 reference categories; female, non-smokers, no family history, no previous surgical treatment

482 **FIGURE LEGENDS**

483

484 **Figure 1. Response after 12 weeks of treatment**

485 **A. DLQI, B. IHS4, C. NRS Pain, D. NRS Pruritus**

486 DLQI; Dermatology Quality of Life Index, IHS4; International Hidradenitis Suppurativa Scoring System, NRS;
487 Numerical rating scale. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

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488 **Table 1. Baseline characteristics**

	Tetracyclines n=180		Clindamycin and Rifampicin n=103		p-value
<u>Patient characteristics</u>					
Gender					
Females, n (%)	106	(58.9)	56	(54.4)	0.533
Age, median [IQR]					
Missing, n	37	[26-46]	36	[27-45]	0.917
	0		1		
Age of onset, median [IQR]					
Missing, n	21	[15-30]	21	[16-28]	0.854
	3		0		
Disease duration, median [IQR]					
Missing, n	10	[6-19]	10	[5-17]	0.415
	3		1		
BMI, mean (SD)					
Missing, n	29.81	(6.1)	29.21	(6.2)	0.428
	6		0		
Current smoker, n (%)					
Missing, n	110	(61.8)	56	(56.6)	0.443
	2		4		
Family history of HS, n (%)					
Missing, n	58	(34.3)	34	(35.1)	1.000
	11		6		
Previous surgical treatment, n (%)					
Missing, n	69	(38.3)	39	(38.6)	1.000
	0		2		
<u>Patient reported outcomes</u>					
DLQI, mean (SD)					
Missing, n	13.3	(7.5)	15.1	(7.9)	0.071
	8		7		
NRS Pain, median [IQR]					
Missing, n	6	[4-8]	7	[5-8]	0.005
	7		3		
NRS Pruritus, median [IQR]					
Missing, n	3	[0-6]	4	[0-7]	0.204
	13		8		
<u>Physician scores</u>					
Inflammatory nodules, median [IQR]					
	3.5	[1.0-6.0]	4	[2-9]	0.029
Abscesses, median [IQR]					
	0.0	[0.0-2.0]	0	[0-2]	0.975
Draining sinus tracts, median [IQR]					
	1.0	[0.0-2.0]	1	[0-4]	0.003
Hurley stage					
Stage I, n (%)	54	(30.2)	14	(13.6)	0.004
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)	0.004
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]					
Mild, n (%)	9.0	[5.0-18.5]	13.0	[6.0-27.0]	0.019
Moderate, n (%)	29	(16.1)	8	(7.8)	0.032
Severe, n (%)	77	(42.8)	38	(36.9)	
	74	(41.1)	57	(55.3)	
Modified Sartorius, median [IQR]					
Missing, n	25.5	[17.0-44.0]	40.0	[26.0-59.0]	<0.001
	38		46		

489 BMI; body mass index, HS; Hidradenitis Suppurativa, DLQI; Dermatology Quality of Life Index, NRS; Numerical rating scale, IHS4; International Hidradenitis Suppurativa Scoring System.

491 **Table 2. Response to treatment after 12 weeks**

	Tetracyclines n= 180		p-value*	Clindamycin & Rifampicin n=103		p-value*	p-value^
<u>Patient reported outcomes</u>							
DLQI, mean (SD)	10.2	(8.2)	<0.001	9.8	(7.6)	<0.001	
Missing, n	7			3			
DLQI MCID achieved, n (%)	58	(36.3)		44	(47.3)		0.084
Missing, n	20			10			
NRS Pain, median [IQR]	4.0	[1.5-7.0]	<0.001	3	[0.0-5.5]	<0.001	
Missing, n	4			3			
NRS Pain MCID achieved	58	(59.8)		51	(63.8)		0.643
Missing, n	83			23			
NRS Pruritus, median [IQR]	1.0	[0.0-5.0]	<0.001	1.0	[0.0-5.0]	<0.001	
Missing, n	12			8			
<u>Physician scores</u>							
Inflammatory nodule count, median [IQR]	2.0	[0.0-4.0]	<0.001	2.0	[0.0-4.0]	<0.001	
Abscess count, median [IQR]	0.0	[0.0-1.0]	<0.001	0.0	[0.0-1.0]	0.001	
Draining sinus tract count, median [IQR]	0.0	[0.0-2.0]	<0.001	1.0	[0.0-2.0]	<0.001	
IHS4, median [IQR]	5.0	[2.0-12.0]	<0.001	6.0	[1.0-17.0]	<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]	<0.001	25.0	[13.0-44.0]	<0.001	
Missing, n	41			45			
HiSCR achieved	55	(40.1)		40	(48.2)		0.263
Missing due to baseline count <3, n	43			20			
<u>Discontinuation and side effects</u>							
Discontinuation	19	(10.7)		16	(15.8)		0.260
Missing, n	3			2			
GI side effects not leading to discontinuation	24	(16.4)		10	(11.8)		0.346
Missing	34			18			

DLQI; Dermatology Quality of Life Index, MCID; minimal clinically important difference, NRS; Numerical rating scale, IHS4; International Hidradenitis Suppurativa Scoring System, HiSCR; Hidradenitis Suppurativa Clinical Response.* compared with baseline scores, ^ comparison of tetracycline and clindamycin + rifampicin groups

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499 **Table 3. 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
<u>Tetracyclines</u>	n=54*	n=90*	n=35*		n=29	n=77	n=74	
HiSCR achieved, n (%)	15 (39.5)	30 (41.7)	10 (37.0)	0.920	5 (41.7)	20 (34.5)	30 (44.8)	0.495
Missing, n	16	18	8		17	19	7	
MCID DLQI achieved, n (%)	20 (41.7)	28 (35.4)	10 (31.3)	0.629	9 (31.0)	25 (32.5)	24 (34.3)	0.901
Missing, n	6	11	3		6	10	4	
MCID Pain achieved, n (%)	13 (41.9)	29 (64.4)	16 (76.2)	0.028	3 (23.1)	19 (51.4)	36 (76.6)	0.001
Missing, n	23	45	14		16	40	27	
<u>Clindamycin + Rifampicin</u>	n=14	n=58	n=31		n=8	n=38	n=57	
HiSCR achieved, n (%)	3 (37.5)	24 (51.1)	13 (46.4)	0.807	1 (25.0)	12 (48.0)	27 (50.0)	0.796
Missing, n	6	11	3		4	13	3	
MCID DLQI achieved, n (%)	6 (54.5)	25 (49.0)	13 (41.9)	0.763	2 (33.3)	16 (47.1)	26 (49.1)	0.843
Missing, n	3	7	0		2	4	4	
MCID Pain achieved, n (%)	5 (62.5)	28 (62.2)	18 (66.7)	0.941	2 (40.0)	17 (58.6)	32 (69.6)	0.357
Missing, n	6	13	4		3	9	11	

MCID; minimal clinically important difference, DLQI; Dermatology Quality of Life Index, HiSCR; Hidradenitis Suppurativa Clinical Response. * Hurley stage missing for 1 patient on tetracyclines.

501 **Table 4. 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)	0.243	253	1.58 (0.94-2.65)	0.085	177	1.18 (0.64-2.18)	0.590
Patient characteristics									
Gender*	220	1.03 (0.60-1.77)	0.910	253	0.98 (0.59-1.62)	0.928	177	0.97 (0.52-1.79)	0.915
Age	219	1.02 (1.00-1.04)	0.051	252	1.00 (0.99-1.03)	0.395	177	1.03 (1.00-1.05)	0.042
Age of onset	218	1.02 (0.99-1.05)	0.126	250	1.00 (0.98-1.03)	0.855	176	1.03 (1.00-1.07)	0.051
Disease duration	217	1.02 (0.99-1.05)	0.291	249	1.01 (0.99-1.04)	0.257	176	1.00 (0.98-1.03)	0.782
BMI	215	0.99 (0.95-1.04)	0.786	247	0.96 (0.96-1.04)	0.799	173	1.00 (0.94-1.05)	0.858
Smoking status*	218	1.35 (0.78-2.36)	0.286	250	1.34 (0.80-2.27)	0.271	174	2.03 (1.09-3.80)	0.026
Family history of HS*	208	1.02 (0.57-1.81)	0.955	238	1.07 (0.62-1.83)	0.820	165	1.15 (0.60-2.22)	0.673
Previous surgical treatment*	219	1.14 (0.66-1.96)	0.644	251	1.21 (0.72-2.02)	0.468	175	1.63 (0.86-3.09)	0.138
Patient reported outcome measures at baseline									
DLQI	211	1.04 (1.00-1.07)	0.053	251	1.11 (1.07-1.16)	<0.001	170	1.02 (0.98-1.07)	0.305
NRS Pain	216	1.03 (0.93-1.14)	0.601	250	1.06 (0.97-1.17)	0.215	176	1.01 (0.88-1.16)	0.867
NRS Pruritus	208	1.07 (0.98-1.16)	0.131	240	1.11 (1.03-1.20)	0.009	169	1.07 (0.97-1.18)	0.154
Physician scores at baseline									
Inflammatory nodule count	220	1.06 (1.00-1.12)	0.044	253	1.03 (0.98-1.08)	0.299	177	1.13 (1.05-1.22)	0.002
Abscess count	220	0.96 (0.87-1.07)	0.473	253	1.06 (0.96-1.17)	0.271	177	1.18 (1.02-1.37)	0.026
Draining sinus tract count	220	0.96 (0.87-1.04)	0.340	253	0.92 (0.84-1.00)	0.054	177	1.06 (0.94-1.19)	0.328
Presence of sinus tracts	220	0.90 (0.52-1.54)	0.690	253	0.78 (0.47-1.31)	0.352	177	1.36 (0.73-2.54)	0.332
Hurley stage									
Hurley stage I		<i>reference</i>			<i>reference</i>			<i>reference</i>	
Hurley stage II	220	1.22 (0.71-2.08)	0.475	252	1.03 (0.62-1.70)	0.922	177	1.16 (0.63-2.13)	0.626
Hurley stage III	220	0.93 (0.50-1.72)	0.814	252	0.80 (0.44-1.44)	0.459	177	1.75 (0.86-3.57)	0.125
IHS4	220	1.00 (0.98-1.01)	0.677	253	0.99 (0.98-1.01)	0.331	177	1.03 (1.01-1.05)	0.017
Mild		<i>reference</i>			<i>reference</i>			<i>reference</i>	
Moderate	220	0.74 (0.42-1.28)	0.281	253	1.02 (0.61-1.70)	0.941	177	0.63 (0.34-1.17)	0.139
Severe	220	1.43 (0.83-2.45)	0.194	253	1.03 (0.62-1.70)	0.916	177	2.85 (1.52-5.34)	0.001
Modified Sartorius	161	0.99 (0.98-1.00)	0.100	183	0.99 (0.98-1.00)	0.054	122	1.00 (0.98-1.01)	0.603

OR; Odds ratio, MCID; minimal clinically important difference, DLQI; Dermatology Quality of Life Index, NRS; Numerical rating scale, BMI; body mass index, IHS4; International Hidradenitis Suppurativa Scoring System. * reference categories; female, non-smokers, no family history, no previous surgical treatment

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508 **Supplemental Table 1. Identification of factors associated with response to**
509 **tetracyclines**

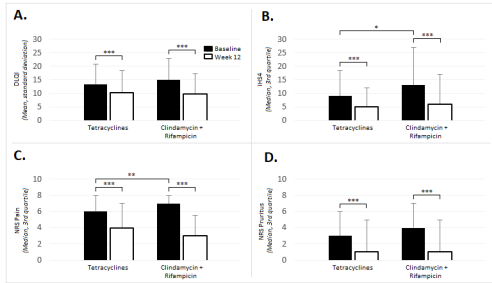
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512 **Supplemental Table 2. Identification of factors associated with response to**
513 **clindamycin and rifampicin**
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CAPSULE SUMMARY

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